DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Secretary's Advisory Committee on
Human Research Protections
Washington, DC 20201

MAR 30 2012

The Honorable Kathleen Sebelius
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Ms. Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration recommendations relevant to the Department of Health and Human Services (HHS) human subjects protection regulations at 45 CFR part 46. These recommendations, stemming from the SACHRP subcommittee on Harmonization, were passed by SACHRP at their February 2012 meeting.

Recommendations from the Subcommittee on Harmonization

On October 28, 2009, SACHRP approved a recommendation establishing a Subcommittee on Harmonization (SOH). SACHRP's charge to this subcommittee was to identify and prioritize areas in which regulations and/or guidelines for human subjects research adopted by various agencies or offices within HHS would benefit from harmonization, consistency, clarity, simplification and/or coordination. The Subcommittee will develop recommendations for consideration and possible adoption by SACHRP, to harmonize and simplify these guidelines and regulations. The goal of this subcommittee effort is to reduce unnecessary burdens on research efforts, thus resulting in better allocation of research resources and promoting the safety and welfare of human subjects.

SACHRP approved the following recommendations and comment from this subcommittee on February 28 and 29, 2012:

Recommendation on Applicability of FDA Regulations for IRBs
(Attachment A)

Recommendation on Single Patient Treatment Use (Attachment B)

Recommendation on Protocol Deviations (Attachment C)

Recommendation Regarding Oversight of Research Misconduct and Regulatory Noncompliance (Attachment D)

Recommendation on Component Analysis

In addition to the recommendations contained in the above attachments, SACHRP addressed the topic of component analysis and heard from experts regarding the historical basis, ethical underpinning, and IRB considerations surrounding this important issue. Although component analysis is generally understood to mean the individual assessment of benefit and risk of each intervention or procedure in a study, the literature on the topic is sparse and complicated, and the regulatory status of the concept is not clear.

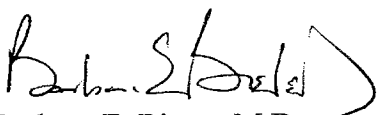
SACHRP recommends that FDA and OHRP issue joint guidance, or if that is not feasible, consistent guidance, explaining how to perform component analysis in the application of Subpart D. Such guidance should include:

1. How to apply 50.51 (404), 50.53 (406), and 50.52 (405) to controlled trials and specifically to placebo-controlled trials,
2. How component analysis does or does not apply to social and behavioral research,
3. How component analysis might impact parental permission and child assent and
4. What documentation from the IRB must be or should be included.

Furthermore, SACHRP recommends that education and training materials for IRB members and investigators be made available and a communication plan developed.

On behalf of SACHRP, I would like to thank you for your consideration of this report. The committee, the Subpart A Subcommittee and the Subcommittee on Harmonization have been actively working in pursuit of their charges, and we look forward to continuing this work to enhance human subjects protections for the benefit of all Americans.

Sincerely,



Barbara E. Bierer, M.D.
Chair, Secretary's Advisory Committee
on Human Research Protections
(SACHRP)

cc: Jerry Menikoff, M.D., J.D., Executive Secretary, SACHRP
Julia Gorey, J.D., Executive Director, SACHRP

SACHRP Recommendation on Applicability of FDA Regulations for IRBs (21 CFR 56) and Informed Consent (21 CFR 50)

INTRODUCTION

The HHS regulations regarding human subject protection at 45 CFR 46 differ in limited but significant ways from the FDA regulations regarding human subject protection at 21 CFR 50 and 56. When a research activity is governed by both sets of regulations, then there are certain regulatory provisions that are allowable under 45 CFR 46 that are not allowable under 21 CFR 50 and 56, and thus cannot be applied to the research. The most commonly encountered of these regulatory provisions are the application of the exempt research categories at 45 CFR 46.101(b)(1) through (b)(6), the provision for waiver of consent at 45 CFR 46.116(d), and the provision for a waiver of documentation of consent found at 45 CFR 46.117(c)(1). There is considerable difference in opinion and practice among IRBs, investigators, institutions and sponsors as to when the FDA regulations apply to a research project. To use a common example, an investigator wishes to conduct a retrospective record review of medical records to determine whether drug X had a better outcome than drug Y for arthritis. Some IRBs will consider this to be non-FDA regulated research that is exempt from IRB review and informed consent based on HHS regulation 45 CFR 46.101(b)(4). Other IRBs will consider this to be non-FDA regulated research that needs IRB review but qualifies for a waiver of consent. Finally, a third set of IRBs will determine that this is an FDA regulated clinical investigation that requires IRB review and informed consent under 21 CFR Parts 50 and 56. This is not uncommon, and there are many such examples, as discussed below. OHRP maintains a registration system for IRBs that conduct either HHS funded or supported research or FDA regulated research. If an IRB reviews both types of research, then it must register with both agencies using that system. As of February 3, 2012, there are 2,308 IRBs that are registered with both OHRP and FDA. All of these IRBs face this issue of determining regulatory applicability on a regular basis.

Therefore, SACHRP recommends the issuance of guidance that will provide regulated parties with objective criteria for determining when a research project is under FDA jurisdiction. As represented in the Venn diagram in Appendix II of this recommendation, the goal of this guidance is to clarify the bottom intersecting line, which represents the overlap between FDA and HHS jurisdiction.

OHRP has existing guidance that outlines the steps of analysis as to the level of IRB oversight required of research (http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html). In summary, that guidance states that the proper analysis under the HHS regulations is:

- Is the activity research?
- Is the activity research involving human subjects?
- Is the activity research that is exempt under 45 CFR 46.101(b)(1) through (6)?
- Is the activity research that can be reviewed through expedited procedures?
- Is the activity research that requires review by a convened IRB?

However, much research is also potentially under FDA jurisdiction. Thus, IRBs could use similar guidance from FDA regarding the definitions of clinical investigation and human subject under the FDA regulations. Ideally, this guidance could be combined with current OHRP guidance on how to determine the status of research under the Common Rule, so that the many IRBs that are registered with both OHRP and FDA would have a single source of guidance on this difficult issue. The result of such guidance would be increased consistency among IRBs and other regulated parties, and subsequently reduced administrative burden on the research community. In addition, if HHS moves forward with the implementation of a Notice of Proposed Rule Making (NPRM) to change the human subject protection regulations, this guidance will provide important public input to OHRP and FDA to proactively consider the relationship between the two sets of regulations and provide clarity on these and similar issues of inconsistency that arise.

RESOLUTION THROUGH GUIDANCE CLARIFYING REGULATORY DEFINITIONS

SACHRP believes that the source of much of the variability of interpretation of the applicability of the FDA regulations stems from the fact that FDA regulations for informed consent (21 CFR Part 50), IRBs (21 CFR Part 56), investigational drugs (21 CFR Part 312), and investigational devices (21 CFR Part 812) contain three different definitions of "human subject," four different definitions of "clinical investigation," and four different definitions of "study article" or its equivalent. These different definitions are provided in Appendix I. It is unclear to the regulated community how to interpret these different definitions, to whom each definition applies, and how the different definitions interact. For instance, it is not clear whether the definitions of "clinical investigation" in 21 CFR Part 50 and 56 are narrower or broader in scope than those in Parts 312 and 812, and when each definition is applicable.

Because these different definitions exist within the FDA regulations, it is difficult to use the same pattern for an algorithm of when the FDA regulations apply. Such an algorithm would follow this order:

- Is the activity a clinical investigation?
- Is the activity a clinical investigation involving human subjects?
- Is the activity exempt under 21 CFR 56.104(a) through (d)?
- Is the activity a clinical investigation that can be reviewed through expedited procedures?
- Is the activity a clinical investigation that requires review by a convened IRB?

If FDA were able to create and publicize an algorithm of this nature, it would resolve many of the issues noted above. SACHRP offers the following thoughts on this issue.

FDA should clarify the interpretation of "clinical investigation" based on the regulatory definitions found in 21 CFR 50, 21 CFR 56, 21 CFR 312, and 21 CFR 812. Each of these four regulations provides a different definition, and it would be very useful to the regulated community if FDA would provide guidance on how these definitions should be interpreted used vis a vis each other and as a whole.[1]

SACHRP notes that the definition of a clinical investigation in 21 CFR Part 56 appears to be the broadest of the four definitions. FDA may find it useful to clarify that Part 56 is the broadest of the definitions and encompasses the other three definitions, and then use it as a platform to provide guidance to the regulated community on the definition of a clinical investigation. For instance, the definition of the term "clinical investigation" in Part 56 says it is an experiment in the broadest sense, and that it is synonymous with terms research, clinical research, clinical study, study, and clinical investigation. Therefore, these terms cannot readily be used to differentiate whether an activity is or is not regulated by FDA under 21 CFR Part 56. FDA may find it useful to clarify this point if in fact there are relevant distinctions between the terms that the regulated community could use to determine whether a given research activity is under FDA jurisdiction.

Two additional criteria in 21 CFR Part 56 that appear critical in determining whether a clinical investigation is regulated by FDA is that the clinical investigation is 1) subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the Food Drug and Cosmetic Act or 2) the clinical investigation is not subject to requirements for prior submission to the FDA under these sections of the Food, Drug and Cosmetic Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. It appears that if the investigator or sponsor must submit the data to FDA, or intends to submit the data to FDA, or FDA might inspect the data, then the clinical investigation (research, study, etc) is regulated by FDA under 21 CFR 56. The "held for inspection" condition seems to be particularly broad and the field would benefit from clarification of this and the other criteria.

FDA should clarify the definition of the terms "involves" and "involving" as they are used in the four definitions of a clinical investigation. FDA could clarify whether a test article has to be

[1] As a model, FDA may wish to consider the May 2011 FDA Draft Guidance for Clinical Investigators, Industry, and FDA Staff on Financial Disclosure by Clinical Investigators, in which the FDA included in the FAQ section questions such as: "How does the definition of 'clinical investigator' in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND regulations (21 CFR part 312)?" and "How does the definition of 'clinical investigator' in the financial disclosure regulation (21 CFR part 54) relate to the definition in the medical device regulations (21 CFR part 812)?" This type of comparison is very useful.

physically used in the research activity for it to be considered an FDA regulated clinical investigation, or whether alternatively the study can "involve" a test article merely by studying existing data, such as medical records, about the use of the product. This point would help to clarify whether retrospective medical records reviews should be considered to be FDA regulated clinical investigations.

Another difference between the definitions is that under 21 CFR Part 312 any use of a drug, except for the use of a marketed drug in the course of medical practice, is a clinical investigation. However, under 21 CFR Part 812 there is only a clinical investigation when the purpose is to study the safety or effectiveness of the device. FDA should clarify how these two different definitions should be interpreted, particularly as they interact with the definitions of "clinical investigation" in 21 CFR Parts 50 and 56.

In order to provide FDA with a starting point in considering this approach, SACHRP provides the following recommendations on the interpretation of the regulatory definitions:

1. FDA should issue guidance stating that the definition of a clinical investigation at 21 CFR Part 56.102(c) is the broadest statement of FDA's interpretation of a clinical investigation, and encompasses the definitions of a clinical investigation in Parts 50, 312, and 812. As such, IRBs and investigators should use the definition in Part 56 for determinations of whether a given project meets the definition of a clinical investigation.

2. FDA should clarify that even though Part 56 states that "The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part," in fact the definition of research at 45 CFR 46.102(d) is a completely distinct regulatory definition that is not synonymous with the definition of a clinical investigation.

3. FDA should clarify the clause in 21 CFR Part 56.102(c) that states that a clinical investigation, "either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit." FDA should clarify whether this clause causes retrospective record reviews, interviews and questionnaires to become FDA regulated clinical investigations if the intent is to submit the data to FDA or hold the data for FDA inspection. SACHRP recommends that FDA clarify that retrospective record reviews, even when regarding the safety and efficacy of a study article, do not qualify as FDA-regulated clinical investigations. If FDA were to interpret the definition of a clinical

investigation such that any retrospective records review involving a regulated study article is a clinical investigation, and therefore that consent is required, much research would not be possible to conduct due to the inability to obtain consent, and the creation of medical knowledge would be significantly curtailed.

4. FDA should clarify the definitions of the terms "involves" and "involving," as they are used in the definition of a clinical investigation in 21 CFR Part 56, related to whether the data will be submitted to FDA or held for FDA inspection, as described in the recommendation above.

5. FDA should clarify whether the definition of human subject should include consideration of whether or not the data are identifiable. If a link is not maintained, or there is only a one-way link, then perhaps the humans would not be subjects under the FDA definition of a human subject. If a link is maintained, at what point do they become human subjects under the FDA definitions?

6. Finally, we believe that FDA should further publicize that the definition of "human subject" is limited to living individuals, and does not include dead individuals. The recent March 2011, FDA guidance entitled "Exception from Informed Consent Requirements for Emergency Research" clarified this issue, but if FDA provides guidance on the definition of a clinical investigation, it would also be a practical location to provide better public visibility of this FDA interpretation.

RESOLUTION THROUGH GUIDANCE ON SPECIFIC ISSUES

As an alternate approach to issuing guidance clarifying the regulatory definitions of clinical investigation, human subject, and study article, as discussed above, FDA may find it more practical and useful to issue guidance on specific examples instead. SACHRP therefore provides the following specific issues and cases that cause confusion as to whether they are FDA regulated clinical investigations.

Retrospective Record Reviews

There is great diversity of opinion among the regulated community as to whether retrospective records reviews are or are not FDA regulated clinical investigations. These retrospective reviews can involve a variety of source data, such as patients' medical records, insurance company records, and publicly available sources such as the Centers for Disease Control (CDC) Death Index. Depending on how the data is collected and recorded, such research may qualify as exempt from the requirements of 45 CFR 46 under the exemption at 46.102(b)(4), may qualify as research not including human subjects under the OHRP "Guidance on Research Involving Coded

Private Information or Biological Specimens," or may qualify for a waiver of informed consent under 45 CFR 46.116(d). However, if the research qualifies as an FDA regulated clinical investigation, then IRB review is required and consent cannot be waived. The practical effect of applying FDA jurisdiction to these studies means that many of them would become impossible or impractical to conduct due to the requirement for informed consent. FDA should issue guidance clarifying whether, and if so, under what circumstances retrospective record reviews qualify as FDA regulated clinical investigations.

SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying when, if ever, retrospective record reviews qualify as an FDA-regulated clinical investigation. SACHRP recommends that FDA clarify that retrospective record reviews, even when regarding the safety and efficacy of a study article, do not qualify as FDA-regulated clinical investigations. The guidance should supply a clear rationale so that regulated entities can apply that rationale to specific cases. Furthermore, SACHRP recommends that FDA establish a standard that strikes the best balance for the public good by promoting the discovery and availability of useful medical knowledge while to the extent necessary providing FDA with control over claims of safety and efficacy of FDA regulated products.

Collection of Data for Purposes other than Establishing Safety and Efficacy of Products

FDA should clarify when the use of data generated as part of medical practice is a "clinical investigation." For example, institutions and physicians often implement quality improvement activities that are intended to improve the quality of patient care, and collect patient or provider data regarding the implementation of the practice for clinical, cost analysis, or administrative purposes. FDA should clarify whether such activities could ever qualify as clinical investigations, and if so, what the determining criteria would be.

SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying that collecting or using medical data for purposes other than establishing the safety and efficacy of test articles is not an FDA regulated activity. Examples provided by FDA should include cost effectiveness and quality improvement.

Drug and Device Registries

FDA should provide guidance clarifying when, if ever, drug and device registries qualify as FDA-regulated clinical investigations, and provide the relevant criteria that cause a registry to be

FDA regulated. Possible criteria that might be addressed include the identity of the individual or entity that establishes and maintains the registry. The guidance should supply a clear rationale so that regulated entities can apply that rationale to specific cases.

SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying whether prospective registries used to collect data regarding the safety and efficacy of FDA regulated test articles are FDA regulated clinical investigations, particularly when the study article is not prescribed or used as a result of the existence of the registry. FDA should consider whether certain types of registries, such as registries designed to collect data on fetal exposure to approved drugs through the mother's use during pregnancy, in which the data is collected through voluntary reporting by the physician or the mother, should be considered FDA-regulated clinical investigations, as this data collection cannot be effectively conducted under FDA regulations due to the difficulty of obtaining informed consent.

Risk Evaluation and Mitigation Strategies

FDA should provide guidance clarifying whether and when risk evaluation and mitigation strategies qualify as FDA regulated clinical investigations. [AJ will state the problem]

SACHRP provides the following recommendation:

FDA should issue guidance clarifying that risk evaluation and mitigation strategies are not FDA regulated clinical investigations, unless the study article is prescribed or used as a result of the existence of the risk evaluation and mitigation strategy.

Training Activities

Training activities also often raise questions of FDA jurisdiction. These training activities may involve medical providers or subjects. It would be useful if FDA provided guidance regarding various training activities clarifying whether or not FDA considers the training activities to be clinical investigations:

a. Research to evaluate the effects of training on the administration or use of test articles such as drugs and devices.
b. Training activities regarding regulated products that are mandated by FDA.
c. Training on how to use a device or drug.

SACHRP provides the following recommendation:

FDA should issue guidance clarifying that training activities that are conducted as part of an FDA regulated clinical investigation fall within the FDA regulated investigation. However, training activities that occur separately from an FDA regulated clinical investigation are not, in and of themselves, a clinical investigation unless they involve use of a test article, a human subject, and data are going to be submitted to FDA or held for FDA. Therefore, an IRB can apply the exemption at 45 CFR 46.102(b) to such training activities if appropriate.

Interviews and Questionnaires

FDA should issue guidance on whether interviews and questionnaires that are administered to medical providers and subjects are FDA regulated clinical trials when they are separate from a clinical investigation. When interviews and questionnaires are administered as part of clinical investigation, they fall within the scope of that investigation. However, sponsors or other parties at times wish to administer interviews or questionnaires separately from a clinical investigation.

SACHRP provides the following recommendation:

FDA should issue guidance clarifying that interviews and questionnaires that are administered to medical providers and subjects separate from FDA regulated clinical trials are not by themselves FDA regulated clinical investigations unless the interview/questionnaire also involves the use of the test article, a human subject, and the data will be submitted to FDA or held for FDA inspection. Therefore, an IRB can apply the exemptions at 45 CFR 46.102(b) to such interviews and questionnaires if appropriate.

Studies of Surgical Techniques

An issue of confusion among IRBs is the applicability of FDA regulations to studies of surgical techniques. It is commonly stated that FDA does not regulate surgery, including in FDA's guidance entitled "Available Therapy," which states, "Some confusion has arisen regarding whether available therapy refers only to products approved by FDA for the use in question, or whether the term could also refer to products used off-label or to treatments not regulated by FDA, such as surgery."[2] FDA should clarify when a study of a surgical technique is or is not a device study. Because all surgery involves the use of at least one, and often dozens, of devices, it is either the case that all research on surgical techniques is FDA-regulated device research, or there is some criteria by which some research on surgical techniques does not qualify as device research. Also, if FDA determines that some or all research on surgical techniques does qualify as device research, it would be helpful if FDA guidance provided criteria for determining which devices being used in a given study of surgical technique are the devices for which the IRB must make appropriate regulatory device findings. Surgery often involves dozens of devices, including oximeters, scalpels, sutures, chest spreaders, heart-lung bypass, IV pumps, etc. It

[2] online at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126586.htm:

would be burdensome for IRBs and investigators to collect the labeling for each of these devices to determine the regulatory status, particularly in multi-site studies because different investigators would very often be using different oximeters, scalpels, etc.

SACHRP provides the following recommendations:

FDA should issue guidance clarifying that studies of surgical techniques are only clinical investigations of devices when the study evaluates the safety or efficacy of the device. If the study is only to test the new technique and not the device, then it falls outside of the device regulations.

Studies of Devices Intended to Obtain Physiologic Data as Opposed to Information About the Safety and Efficacy of the Device

FDA should clarify that the use of a medical device (e.g., an MRI in behavioral and social science research) when the purpose of the study is to obtain basic physiologic information, rather than to test the safety or effectiveness of the device, is not a clinical investigation.

SACHRP provides the following recommendation:

FDA should clarify that the use of a medical device to obtain basic physiologic information, as opposed to obtaining data regarding the safety or effectiveness of the device, is not a clinical investigation.

CONCLUSION

SACHRP considers the issues presented in this recommendation to be very important. The current lack of clarity of the applicability of FDA regulations causes IRBs, investigators, institutions, and sponsors to apply the FDA regulations inconsistently, causes extensive unnecessary administrative burden and regulatory uncertainty, and may place unnecessary restrictions on valuable research. SACHRP hopes that FDA, OHRP, OCR and other agencies that have adopted the Common Rule will work together to enhance the human subject protection system by addressing these issues.

Appendix I

Relevant Regulations

There are four different definitions of clinical investigation found in 21 CFR 50 and 56, 312, and 812:

21 CFR 50.3(c): Clinical investigation means 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 Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

21 CFR 56.102(c): Clinical investigation means any experiment that involves a test article and one or more human subjects and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

21 CFR 312.3(b): Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

21 CFR 812.3(h): Investigation is a clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.

There are four different definitions of test article (or its equivalent) found in 21 CFR 50 and 56, 312, and 812:

21 CFR 50.3(j): Test article means any drug (including a biological product for human use) medical device for human use, human food additive, color additive, electronic product, or any

other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

21 CFR 56.102(l): Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

21 CFR 312.3(b): Investigational new drug means a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

21 CCFR 812.3(g): Investigational device means a device, including a transitional device, that is the object of an investigation.

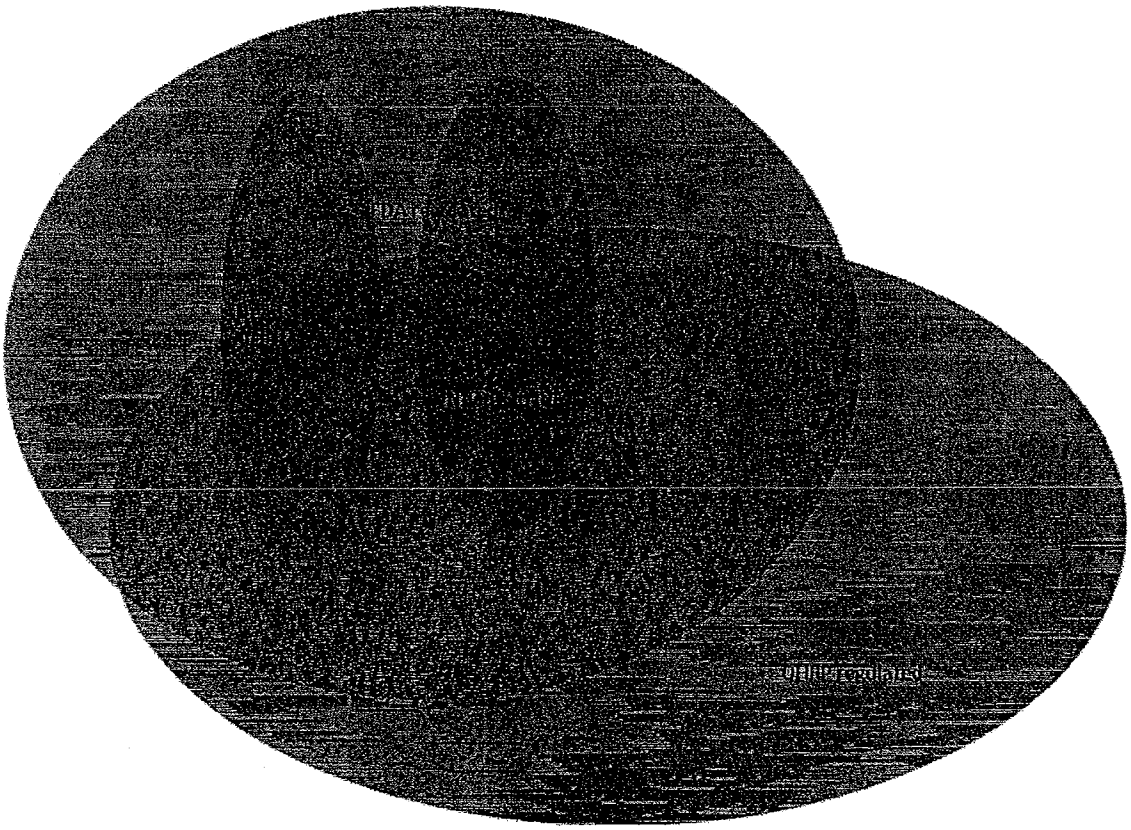
<u>There are three different definitions of human subject found in 21 CFR 50 and 56, 312, and 812.</u>

21 CFR 50.3(g) and 56.102(e): Human subject means an individual who is or becomes a participant in research, either as a recipient of the test articles or as a control. A subject may be either a healthy human or a patient.

21 CFR 312.3(b): Human subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

21 CFR 812.3(p): Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control A subject may be in normal health or may have a medical condition or disease.

Appendix II



SACHRP Recommendations on Single Patient Treatment Use

At the SACHRP meeting of October 4, 2011, FDA representatives asked SACHRP to provide feedback to FDA on several questions regarding treatment use of investigational drugs/biologics for individual patients, as allowed by 21 CFR 312.305 and 312.310. The representatives noted that FDA continues to hear from individual patients, caregivers, IRB members, and health care professionals that the administrative burdens associated with IRB review of expanded access are onerous and diminish its practicality, negatively impacting access to investigational drugs for treatment under expanded access protocols, particularly single patient treatment access protocols. The problem is particularly acute for physicians and patients that seek expanded access outside of institutional settings with an internal IRB.

The questions FDA asked included:

- What is the Committee's experience with IRB reviews of expanded access protocols?
- How quickly are they reviewed?
- Is there a charge to the individual?
- Are expanded access protocols able to be scheduled ahead of studies already on the calendar?
- Does providing for something like expedited IRB review seem a reasonable solution, based on the problem cited?
- If a reduction in the number of IRB members to approve an expanded access protocol is satisfactory to the Committee, does the Committee believe that mimicking the expedited review procedure is the best approach?
- What is the Committee's opinion on the risk/benefit analysis of expanded access protocols following the IRB procedure discussed in this presentation?

SACHRP agrees that substantial barriers exist to access to investigational drugs/biologics for treatment use, and that the problems are exacerbated for physicians and patients outside of an institutional setting. We offer the following comments and suggestions.

SACHRP notes that as a threshold issue, single patient access use does not involve the conduct of "research" as defined at 45 CFR 46 because there is no intent to develop generalizeable knowledge. Rather, this issue arises out of the FDA prohibition on the use of unapproved drugs, which requires that any use of an investigational drug must currently be considered within the regulatory framework for clinical investigations, primarily 21 CFR Parts 50, 56, and 312.

While the application of the FDA regulations regarding treatment use of investigational drugs/biologics for individual patients (21CFR 312.305 and 312.310) at the single site level with

a single patient does not represent research, it is important for IRBs, sponsors and FDA to recognize that the addition of more patients with similar indications begins to raise the need that research related to those indications should occur. Indeed, the Belmont Report is instructive on this point:

> "When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is 'experimental,' in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)" [Belmont Report]

In answer to the first four questions from FDA, the SACHRP and SOH members have had varying experience with IRB review of single patient expanded access protocols. However, despite our disparate experiences, common themes have emerged. First, reviews of treatment use are administratively burdensome because they involve unique documents and require coordination efforts that differ from the standard IRB review processes. As such, they involve extra time from IRB staff, chairs, and members. They are also difficult from an IRB perspective because they differ from the usual IRB function of reviewing research designed primarily to develop knowledge, as opposed to providing treatment to an identified individual patient. As to the time to review, some IRBs, depending on the setting, are able to review single patient expanded access protocols within a day or two. However, particularly in smaller institutional settings, it is often difficult to convene an ad hoc IRB meeting, as small institutions often have only one scheduled IRB meeting per month. In our collective experience, only independent IRBs charge for the review of single patient expanded access protocols, although some of the independent IRBs waive or reduce the standard IRB fee in these situations, either as standard procedure or upon request. In the experience of the membership of SACHRP and SOH, institution-based IRBs do not charge for these reviews, but we cannot confirm that this is universally true. Expanded access protocols can generally be scheduled ahead of other protocols, but more often the problem is one of arranging an ad hoc IRB meeting to review the expanded access protocol rather than moving that protocol ahead of other protocols in the queue for a scheduled IRB meeting.

SACRHP recommends the way to most immediately address this issue without any change to regulation or guidance is FDA issuance of more specific advice on how to obtain access to treatment use protocols. Currently the FDA website offers only limited advice, and to understand and utilize that advice the reader needs to have a solid understanding of the FDA regulations and their administrative support by FDA. The revised advice should provide a complete overview of the entire issue in one place, and should be understandable to physicians who do not normally conduct research and understandable to non-medically trained patients, as

patients and their relatives and loved ones often end up with the task of arranging the expanded access. The advice should include various scenarios. For instance, there are the necessary additional steps to take when the study article is not in the possession of the physician, and must be supplied by the sponsor in a time sensitive nature, and transportation of investigational product must be arranged. The advice should clearly address the role of each party in the process (FDA, sponsor/manufacturer, physician/investigator, IRB, and patient), and delineate in detail what steps must be taken sequentially, and which steps can be taken in any order as long as they are accomplished prior to use of the investigational product. It is often the case that one party or another (FDA, sponsor, investigator) believes that they cannot proceed until one of the other parties takes an action such as providing approval. It would also provide the most immediate assistance in easing the burden of the various parties involved in single patient expanded access protocols if FDA provided a template protocol, consent form, and any other documents necessary for single patient expanded access protocols. Much of the administrative burden associated with these protocols involves the development of such documents, often from scratch, and subsequent communications between the various involved parties to ensure that the documents are sufficient. This undertaking would provide the most immediate assistance in easing the burden of the various parties involved in single patient expanded access protocols, including patients. SACHRP notes that the American Society of Clinical Oncology (ASCO) issued a press release saying that it would provide guidance of this type, but it is not easy to find on the ASCO website[1], nor is it intuitive for all types of products that one should look to that website.

SACHRP believes that access to investigational drugs could be facilitated substantially if FDA continued to adhere to the "substance" of oversight requirements while being flexible as to "form." That is, certain substantive criteria must be met in order to allow expanded access, and these criteria should be assessed, with satisfaction of these elements documented. However, FDA could exercise enforcement discretion as to the form of review and allow individuals, or committees other than IRBs, to conduct this review, provided the review incorporates the required criteria.

This approach would offer greater flexibility to institutions, health care professionals and the patient community and would likely expedite access for patients, without compromising oversight standards. In addition, this more flexible approach may be better received by many IRBs, which are accustomed to reviewing traditional research protocols and sometimes do not feel comfortable or uniquely qualified to evaluate expanded access use. Given the strong federal policy reasons supporting expanded access, a degree of flexibility as to form of review is consistent with the policy and may even enhance it, as access would be facilitated in practice,

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[1] See http://www.asco.org/ASCOv2/Press+Center/Latest+News+Releases/ASCO+News/ASCO+and+FDA+Work+Together+to+Help+Physicians+Secure+Investigational%2C+Unapproved+Drugs+For+Seriously+Ill+Patients+in+Need. SACHRP members were not able to find the resource on the ASCO website.

and substantive oversight would be maintained or even enhanced by the ability to tailor the review appropriately.

SACHRP believes the most efficient means to implement this flexible approach would be to issue guidance allowing the chair of the IRB, or another appropriate board member, to review the expanded access proposal and provide an appropriate opinion. CDRH has already issued guidance to this effect,[2] and if CDER and CBER followed this process as well much of the problem with IRB delay would be resolved.[3] It would need to be clear that this review is not expedited review, and it would be helpful to provide other administrative details, such as whether the single IRB member has the authority to disapprove the expanded use.

Alternatively, a possible approach is to allow IRBs to review treatment use protocols for individual patients through expedited review. SACHRP does not believe that allowing expedited approval of treatment use protocols for individual patients by IRBs is viable unless there is a change to the expedited review regulations at 21 CFR 56.110. In order to be eligible for expedited review, clinical investigations must be minimal risk and must be listed on the separate expedited categories list. These types of test article access rarely involve minimal risk. As the purpose of this access is treatment rather than research, SACHRP believes that a revision to the expedited regulations for this purpose would be a rational approach because, although there may be clinical risks from the treatment, there is no "research risk" involved in such single-patient treatment use.

SACHRP also recommends that there are several alternative approaches the agency might wish to consider. One is to invoke the IRB waiver that currently exists in the FDA regulations at 21CFR56.105. SACHRP recommends that FDA develop a form or format that a treating physician could file with FDA as a "sponsor-investigator" that would request a waiver of IRB review. FDA could develop a process of automatic approval or approval after a brief review of the form. It would be appropriate for the FDA to require the treating sponsor-investigator to notify the IRB with 5 days of such use and to require some form of patient consent as an additional safeguard.

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[2] Guidance on IDE Policies and Procedures, Chapter III, online at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf.

[3] SACHRP suggests that a change to existing FDA guidance would be useful in accomplishing this. Currently, the Information Sheet entitled "Emergency Use of an Investigational Drug or Biologic" states that "The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval." On-line at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm. Many IRBs interpret this as not allowing a single board member to review single patient expanded access protocols.

Another approach would be to create ready access to a designated single patient access IRB. FDA's existing internal IRB could be that designated IRB. As an alternative to using FDA's internal IRB, FDA could provide a contract or special designation to an existing IRB, but regulatory authority and funding issues would need to be addressed.

Finally, SACHRP notes that FDA could modify 21 CFR 312 so that IRB review of single patient expanded access protocols is not required.

Finally, SACHRP recommends that FDA consider alteration of the current informed consent requirements for clinical investigations when applied to single patient expanded access protocols. Several of the elements of consent do not seem to apply to these protocols.

Regardless of the approach that FDA adopts, FDA and OHRP must work together to ensure that OHRP agrees to the approach.

SACHRP would be pleased to provide further information or opinion on any of the above issues if the input would be of value to the FDA. Patient access to investigational treatments is an critical issue, involving important and difficult principles such as protection of patients from unsafe and ineffective products, while at the same time allowing access for desperately ill patients who have exhausted other options.

Appendix of Relevant Regulations and Guidance

FDA Regulations

21 CFR 312, Subpart I - **Expanded Access to Investigational Drugs for Treatment Use**

Sec. 312.300 General.

(a) *Scope* . This subpart contains the requirements for the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

(b) *Definitions* . The following definitions of terms apply to this subpart:

Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Sec. 312.305 Requirements for all expanded access uses.

The criteria, submission requirements, safeguards, and beginning treatment information set out in this section apply to all expanded access uses described in this subpart. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access are described in 312.310 through 312.320.

(a) *Criteria* . FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context

of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

(b) *Submission* . (1) An expanded access submission is required for each type of expanded access described in this subpart. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

(2) The expanded access submission must include:

(i) A cover sheet (Form FDA 1571) meeting the requirements of 312.23(a);

(ii) The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;

(iii) The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;

(iv) The method of administration of the drug, dose, and duration of therapy;

(v) A description of the facility where the drug will be manufactured;

(vi) Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;

(vii) Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

(viii) A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

(3) The expanded access submission and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

(c) *Safeguards* . The responsibilities of sponsors and investigators set forth

in subpart D of this part are applicable to expanded access use under this subpart as described in this paragraph.

(1) A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use under this subpart is considered an *investigator* , for purposes of this part, and must comply with the responsibilities for investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(2) An individual or entity that submits an expanded access IND or protocol under this subpart is considered a *sponsor* , for purposes of this part, and must comply with the responsibilities for sponsors set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(3) A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access use under this subpart is considered a *sponsor-investigator* , for purposes of this part, and must comply with the responsibilities for sponsors and investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(4) *Investigators* . In all cases of expanded access, investigators are responsible for reporting adverse drug events to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter, and maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of 312.62. Depending on the type of expanded access, other investigator responsibilities under subpart D may also apply.

(5) *Sponsors* . In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by 312.32 and 312.33, ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use, providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (the investigator's brochure must be provided if one exists for the drug), maintaining an effective IND for the expanded access use, and maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of 312.57. Depending on the type of expanded access, other sponsor responsibilities under subpart D may also apply.

(d) *Beginning treatment* --(1) *INDs* . An expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin.

(2) *Protocols* . With the following exceptions, expanded access use under a protocol submitted under an existing IND may begin as described in 312.30(a).

(i) Expanded access use under the emergency procedures described in 312.310(d) may begin when the use is authorized by the FDA reviewing

official.

(ii) Expanded access use under 312.320 may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin.

(3) *Clinical holds* . FDA may place any expanded access IND or protocol on clinical hold as described in 312.42.

Sec. 312.310 Individual patients, including for emergency use.

Under this section, FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

(a) *Criteria* . The criteria in 312.305(a) must be met; and the following determinations must be made:

(1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

(2) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

(b) *Submission* . The expanded access submission must include information adequate to demonstrate that the criteria in 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of 312.305(b).

(1) If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.

(2) A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.

(3) A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

(c) *Safeguards* . (1) Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy.

(2) At the conclusion of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.

(3) FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.

(4) When a significant number of similar individual patient expanded access

requests have been submitted, FDA may ask the sponsor to submit an IND or protocol for the use under 312.315 or 312.320.

(d) *Emergency procedures* . If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. The FDA reviewing official may authorize the emergency use by telephone.

(1) Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, 301-827-1800 or 1-800-835-4709, e-mail:*ocod@fda.hhs.gov* . For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301-796-3400, e-mail:*druginfo@fda.hhs.gov* . After normal working hours (8 a.m. to 4:30 p.m.), the request should be directed to the FDA Emergency Call Center, 866-300-4374, e-mail:*emergency.operations@fda.hhs.gov* .

(2) The licensed physician or sponsor must explain how the expanded access use will meet the requirements of 312.305 and 312.310 and must agree to submit an expanded access submission within 15 working days of FDA's authorization of the use.

[74 FR 40942, Aug. 13, 2009, as amended at 75 FR 32659, June 9, 2010]

FDA Guidance on Treatment Use for Drugs and Biologics:

Emergency Use of an Investigational Drug or Biologic - Information Sheet

Guidance for Institutional Review Boards and Clinical Investigators

The emergency use of test articles frequently prompts questions from Institutional Review Boards (IRBs) and investigators. This information sheet addresses three areas of concern: emergency Investigational New Drug (IND) requirements; IRB procedures; and informed consent requirements.

Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test

article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means [21 CFR 312.310(d)].

FDA Contacts for Obtaining an Emergency IND

Product	Office/Division to Contact
drug products	Division of Drug Information[1] (888) 463-6332 (301) 796-3400
biological blood products	Office of Blood Research and Review (HFM-300) (301) 827-3518
biological vaccine products	Office of Vaccines Research (HFM-400) (301) 827-3070
On nights and weekends	Office of Crisis Management & Emergency Operations Center (866) 300-4374 (301) 796-8240

Emergency Exemption from Prospective IRB Approval

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second

individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below.

- **Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
- **Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Institutional procedures may require that the IRB be notified prior to such use, however, this notification should not be construed as an IRB approval. Notification should be used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, some IRBs have sent to the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although, this is not an "IRB approval," the acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

This policy is undergoing review and is subject to change.

Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.

3. Time is not sufficient to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

Exception from Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived, is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are usually not eligible for the emergency approvals described above. The information sheet "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble," is a compilation of the wording of 21 CFR 50.24 and pertinent portions of the preamble from the October 2, 1996 Federal Register.

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm

FDA Guidance on Treatment Use for Devices:

Chapter III
Expanded Access to Unapproved Devices

According to the statute and FDA regulations, an unapproved medical device may normally only be used on human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity, or to help a patient suffering from a serious disease or condition for which there exists no other alternative therapy. Below is a discussion of the four main mechanisms by which FDA may make unapproved devices available to patients/physicians faced with circumstances such as those described. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (See section 561 of the Federal Food, Drug, and Cosmetic Act). FDA plans to modify existing guidance in minor ways, as needed, to track the language in the new law.

Emergency Use of Unapproved Medical Devices
Procedures governing the emergency use of an investigational device are covered in two separate

documents: the IDE regulation (21 CFR Part 812) and FDA's "Guidance for the Emergency Use of Unapproved Medical Devices," (hereinafter referred to as the Emergency Use Guidance) which appeared in the **Federal Register** of October 22, 1985 (50 FR 42866).

The IDE regulation recognizes that emergency situations may arise in which there will be a need to use an investigational device in a manner inconsistent with the approved investigational plan or by a physician who is not part of the clinical study. Therefore, the regulation permits deviations from the investigational plan when necessary to protect the life or physical well-being of a subject in an emergency. (See 21 CFR 812.35(a)). Prior approval for shipment or emergency use of the investigational device is not required, but the use should be reported to FDA by the IDE sponsor via a supplement within 5 working days from the time the sponsor learns of the use. The supplement should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed (as discussed below), and patient outcome information. In addition to the IDE regulation, emergency use is also addressed in an FDA guidance document.

The Agency issued the Emergency Use Guidance because the IDE regulation does not address emergency use comprehensively (e.g., by not defining the term "emergency use," identifying the patient protection measures that should be followed in such situations, or addressing emergency use of devices not covered by an IDE). This guidance defines an unapproved medical device as a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e)(the act) or an approved IDE under section 520(g) of the act (21 U.S.C. 360j(g)). As discussed in the Guidance, an unapproved device should normally only be used in human subjects if it is approved for clinical testing under an IDE and if it is used by an investigator for the sponsor in accordance with the terms and conditions of the application. 18Emergency use of an unapproved device, however, may also occur when: (i) an IDE for the device does not exist, (ii) when a physician wants to use the device in a way not approved under the IDE, or (iii) when a physician is not an investigator under the IDE.

The Emergency Use Guidance document was intended to address these *emergency* situations. As stipulated in the guidance, a physician who intends to treat a patient with an unapproved medical device in an emergency situation should conclude that:

1. The patient has a life-threatening condition that needs immediate treatment.†
2. No generally acceptable alternative treatment for the condition exists; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

1. Informed consent from the patient or a legal representative;

2. Clearance from the institution as specified by their policies;
3. Concurrence of the IRB chairperson;
4. An independent assessment from an uninvolved physician; and
5. Authorization from the IDE sponsor, if an approved IDE exists for the device.

Although not provided for under this guidance, often times a physician, who is faced with an emergency situation as described above, will contact FDA to discuss his/her patient's condition. In this situation, ODE acts in an advisory role, rather than in an approving role. The ODE employee who receives the call should discuss the emergency use criteria with the physician, but the responsibility for making the decision as to whether the situation meets the emergency use criteria and whether the unapproved device should be used lies with the physician. If the physician decides to proceed with the emergency use of the device, the ODE employee should advise the physician of the above patient protection procedures to be followed before the emergency use occurs and fill out the Emergency Use Checklist. This checklist helps to ensure that the criteria for emergency use have been met and that the physician has been informed that he/she is expected to follow as many patient protection procedures as possible. After discussing the situation with the physician and completing the checklist, it should be filed in the Emergency Use Report File located in the Program Operations Staff.

After the emergency use occurs, the treating physician is responsible for ensuring that certain follow-up procedures occur. If an IDE exists for the device, the physician should provide the IDE sponsor with sufficient patient follow-up information to allow the sponsor to comply with the reporting requirements of the IDE regulation. If no IDE exists, the physician should submit a follow-up report on the use of the device to the IDE Staff. This report should contain a summary of the conditions constituting the emergency, patient protection measures that were followed, and patient outcome information.

For more information on emergency use of investigational devices, see 50 FR 42866 and 21 CFR812.35(a).

Individual Patient Access to Investigational Devices Intended for Serious Diseases

As discussed above, the IDE regulation and the Emergency Use Guidance address those situations in which an investigational or unapproved device, respectively, is needed to save the life of a patient or to prevent irreversible morbidity. FDA recognizes, however, that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening condition (hereinafter referred to as "compassionate use"). In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur. Unlike emergency use of an unapproved device, prior FDA approval is needed before compassionate use occurs. In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section 812.35(a) in order to treat the patient. The IDE supplement should include:

† As a matter of practice, FDA has expanded the criteria of "life-threatening condition" to include serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity. This is consistent with the new law.

1. A description of the patient's condition and the circumstances necessitating treatment;
2. A discussion of why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;
3. An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and
4. The patient protection measures that will be followed. (These measures were previously discussed under the Emergency Use Guidance.)

The sponsor should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances. (IDE boilerplate G-16A has been developed for reviewers to use when addressing this type of request.) In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.

If the request is approved, the attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device. Following the compassionate use of the device, a follow-up report should be submitted to FDA as an IDE supplement in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, these should be discussed in the supplement and reported to the reviewing IRB as soon as possible.

The above compassionate use criteria and procedures can also be applied when a physician wishes to treat a few patients rather than an individual patient suffering from serious disease or condition for which no alternative therapy adequately meets the medical need. In this case, the physician should request access to the investigational device through the IDE sponsor. The sponsor should submit an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

Treatment Use of Investigational Devices
Provisions of the Regulation

In the **Federal Register** of September 18, 1997 (62 FR 48940), FDA established procedures to allow for the treatment use of investigational devices. These procedures are intended to facilitate the availability of promising new therapeutic and diagnostic devices to desperately ill patients as early in the device development process as possible, i.e., before general marketing begins, and to obtain additional data on the device's safety and effectiveness. These procedures apply to patients with serious or immediately life-threatening diseases or conditions for which no comparable or satisfactory alternative device, drug, or other therapy exists.

Under the final rule, treatment use of an investigational device will be considered when:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and
4. The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

Procedures
If a sponsor is considering submitting a treatment IDE, the sponsor should consult with the appropriate review division in order to determine if the device/indication would meet the criteria for approval. Note that treatment IDEs are limited to those devices/indications which meet the criteria defined above. According to 21 CFR 812.36, requests for treatment use should be submitted as a supplement to the existing IDE and should include:

1. The name, address, and telephone number of the sponsor of the treatment IDE;
2. The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use;
3. An explanation of the rationale for the use of the device, including either a list of the available regimens that ordinarily should be tried before using the device or an explanation of why the use of the device is preferable to the use of available marketed treatments;
4. A description of clinical procedures, laboratory tests, or other measures to be used to monitor the effects of the device and to minimize risk;
5. Written procedures for monitoring the treatment use and the name/address of the monitor;
6. Instructions for use and all labeling for the device as required under section 812.5(a) and (b);
7. Information relevant to the safety and effectiveness of the device for the intended treatment use;
8. A statement of the sponsor's commitment to meet all applicable responsibilities under Parts 812 and 56 and to ensure compliance of all participating investigators with Part 50;
9. An example of the investigator agreement to be signed by all investigators and certification that no investigator will be added to the treatment IDE before the agreement is signed; and
22
10. If the device is to be sold, the price to be charged and a statement that the price is based on manufacturing and handling costs only.

As with all IDEs, treatment IDEs may begin 30 days after FDA receives the application, unless FDA notifies the sponsor earlier than 30 days that the treatment use may or may not begin. The Agency may approve the treatment use as proposed, approve it with modifications/conditions, or disapprove it. FDA may withdraw approval of the treatment IDE if it is determined that the above criteria are no longer met.

In order to protect the rights, safety, and welfare of human subjects involved in the clinical trial,

while at the same time facilitating the development of beneficial device therapies, FDA included certain safeguards in the Treatment IDE process. Some of these measures were already in place as part of the IDE regulation, while other safeguards were specifically designed for treatment use.

Safeguards for this process include: the distribution of the device through qualified experts; maintenance of adequate manufacturing facilities; the submission of reports pursuant to 21 CFR 812.150; and compliance with the regulations governing informed consent and institutional review boards. Sponsors should review these sections of the regulation when preparing a Treatment IDE application to ensure that these issues are properly addressed.

When an IDE supplement requesting approval for treatment use is received in the reviewing division, the reviewer should immediately notify the IDE Staff. The IDE Staff will assist the division with the review of the application to ensure that all applicable safeguards have been satisfied and that all of the criteria identified in the regulation (see above) have been adequately addressed before the application can be approved. Three boilerplate letters are available for responding to requests for treatment use: G-46 for approval, G-47 for conditional approval, and G-48 for disapproval.

ODE review divisions should note that the IDE tracking sheets include a reason-for-submission code for Treatment IDE supplements. It is important that the division indicate on the tracking sheets that the application was a Treatment IDE, so that these applications can be properly tracked.

The Treatment IDE regulation is effective on January 16, 1998. For further guidance on Treatment IDEs, see the **Federal Register** of September 18, 1997 (62 FR 48940) or contact the IDE Staff at (301) 594-1190.

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf.

SACHRP Recommendation on Protocol Deviations

A problematic area in human subject protection is the wide divergence among institutions, sponsors, investigators and IRBs regarding the definition of and the procedures for reviewing protocol deviations.

Focus of the Recommendation

In virtually every research study departures occur from the procedures set forth in the IRB-approved protocol. Various terms are used to describe these departures, including "protocol deviations," "protocol violations," "protocol variances," and "non-compliance." For the purposes of this recommendation, such departures shall be herein referred to as "protocol deviations." Protocol deviations occur for a variety of reasons, such as an investigator's decision to deviate from the protocol, the subject's lack of adherence to the protocol, or external/environmental factors (e.g., severe weather or holidays) that change the performance of a protocol. Some protocol deviations are anticipated and/or intentional; others are not. Some protocol deviations are known or identified before they occur; others are only discovered to have occurred after the fact. The HHS and FDA regulations and guidance are inconsistent in addressing protocol deviations, and even among the various FDA regulations and guidance documents there are inconsistencies. However, as noted below in its central recommendation, SACHRP believes that FDA and OHRP can provide guidance to clarify their currently existing positions on this issue.

This recommendation specifically addresses three types of deviations:

- Deviations that occur because an investigator, research staff or other party involved in the conduct of research intentionally decides to deviate from the approved protocol.
- Deviations from the protocol that are identified before they occur, but cannot be prevented.
- Deviations from the protocol that are discovered after they occur.

Each of these deviations is defined and examples are provided is sections II, III, and IV below. Section V contrasts two other activities from the three types of deviations. These other two activities are:

- Deviations from the protocol performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4).
- Changes in research made in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4).

Both of these activities are outside of the scope of this recommendation.

Section VI provides SACHRP's secondary recommendations regarding the three types of deviations.

I. Current FDA and OHRP Interpretation, and SACHRP's Central Recommendation

The HHS and FDA regulations are inconsistent in addressing protocol deviations. In addition, among the various FDA regulations and guidance there are inconsistencies. However, FDA and OHRP have each indicated in various formats that intentional protocol deviations are changes in research that need prior IRB review and approval. SACHRP's central recommendation is that FDA and OHRP publish a clear statement of their positions regarding intentional protocol deviations. The following are the essential statements of the current FDA and OHRP positions on protocol deviations. (See Appendices I and II for additional background information on existing regulations and guidance.)

FDA Center for Device and Radiologic Health (CDRH):

FDA device regulations explicitly address protocol deviations. 21 CFR 812.150 requires:

> (a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:
> ...
> (4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical wellbeing of a subject in an emergency. ... Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB [approval] in accordance with §812.35(a) also is required.

FDA Center for Drug Evaluation and Research (CDER):

FDA drug regulations do not explicitly address protocol deviations. However, the issue is directly addressed in the FDA "Compliance Program Guidance Manual, Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, December 8, 2008." The manual states:

> Protocol deviations. A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective exception to the protocol (e.g. agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria). Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35(a)(2)), and generally communicated to FDA. "Protocol deviation" is also used to refer to any other, unplanned, instance(s) of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to

complete scheduled visits as required by the protocol, would be considered protocol deviations. Determine whether changes to the protocol were:

i. Documented by an amendment, dated, and maintained with the protocol;
ii. Reported to the sponsor (when initiated by the clinical investigator); and
iii. Approved by the IRB and FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazard(s) to human subjects).

Office for Human Research Protections (OHRP):

OHRP has not issued written guidance on protocol deviations. However, OHRP's unwritten position is that all intentional protocol deviations are changes in research that need prior IRB review and approval before implementation.

At the current time, much of the regulated community is unaware of these positions. SACHRP's central recommendation is that FDA and OHRP issue either joint guidance, or if that is not feasible, separate consistent guidance clearly outlining these positions.
The remainder of this letter contains discussion points and references for FDA and OHRP consideration, and minor recommendations on specific points.

II. Intentional Protocol Deviations

The first focus of this recommendation is deviations that occur because an investigator, research staff or other party involved in the conduct of research intentionally decides to deviate from the approved protocol. Examples of such intentional protocol deviations include the following types of cases:

- Lab criteria: One test is out of range for a benign reason (increased alkaline phosphatase, LDH or SGOT in a runner, or increased bilirubin in a person with Gilbert Syndrome). The investigator decides to enroll the subject despite the out-of-range lab criteria.

- Age criteria: The criteria includes an age requirement of 20-60 years of age, but a potential subject turned 61 a week before screening. The investigator decides to enroll the subject despite being outside of the age range.

- Payment: The protocol specifies that subjects will be paid twenty dollars per visit. To compensate for higher expenses, the investigator decides to pay certain subjects more than other subjects.

- Timing of study visit: At the time of enrollment, the investigator realizes that due to a planned vacation the subject will miss one out of 12 regularly scheduled two-week study visits. The investigator decides to enroll the subject despite this knowledge.

- Timing of washout: A planned vacation interferes with a washout period. Shortening the wash-out period from 14 to 12 days will allow the subject to be enrolled. The investigator decides to enroll the subject with a 12-day washout.

- Pre-treatment exceeded: Protocol entry criteria specify that only a certain amount of pre-treatment of disease is acceptable. A potential subject has exceeded it to a minimal extent. The investigator enrolls the subject despite knowledge of the extent of the pre-treatment.

- Changes to survey instrument: In a behavioral study utilizing a questionnaire, the investigator realizes that two of the questions would work better in reverse order. The investigator re-orders the questions without IRB approval.

In these situations, the investigator or another party decides to deviate from the protocol. Sometimes these intentional protocol deviations are a one-time event. Other times they lead to the implementation of a permanent change to the protocol or other research documents. These intentional protocol deviations may or may not adversely affect the safety, rights and welfare of the research subject, and they may or may not adversely affect the scientific validity of the research.

III. Protocol deviations that are identified before they occur, but cannot be prevented

The second topic of focus for this recommendation is deviations from the protocol that an investigator, research staff and/or other party involved in the conduct of the research are able to identify before they occur, but cannot prevent from occurring. An example is a research subject who is on a business trip and calls the investigator to announce that she is stuck in a snow storm and cannot be at a study visit scheduled for the next day. The investigator knows in advance that the deviation will occur, but it is not under the investigator's control, and it is not the investigator's intent to deviate from the protocol. (See point V.5 below).

IV. Protocol deviations that are discovered after they occur

The third topic of focus for this recommendation is deviations from the protocol that occur because an investigator, research staff and/or other party involved in the conduct of the research deviate from the protocol unintentionally, and such deviations are not identified until after they occur. Examples include an investigator's accidental failure to perform a protocol-required physical, a subject's failure to self-administer or incorrectly administer the test agent, or a coordinator's accidental failure to perform a protocol-required blood test on subjects. These deviations from the protocol were not planned nor intended. These types of deviations must be analyzed upon discovery such that a determination may be made as to the root cause of the deviation, and whether or not such a deviation(s) constitutes an unanticipated problem involving risks to subjects or others and/or constitutes serious or continuing non-compliance.

V. Protocol deviations to eliminate apparent immediate hazards and IRB-approved changes in research

The three protocol deviations described in Sections II-IV that are the focus of this recommendation need to be contrasted from deviations to eliminate apparent immediate hazards

and from IRB-approved changes in research. Both of these activities are already addressed in the regulations and IRBs are required to have written procedures addressing these activities.

Deviations from the protocol performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4): These differ from the protocol deviations as described in the examples above in that these types of deviations are performed in reaction to a perceived hazard, such as the occurrence of an unexpected serious adverse event. They are intentional, but they are done to prevent harm to subjects in a time-sensitive situation, as specifically allowed by the regulations. Thus, they are distinct from the intentional deviations that are the focus of this recommendation.

IRB approved changes in research under 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4): In addition, the protocol deviations that are the focus of this recommendation also need to be contrasted from IRB-approved changes in research. If an intentional protocol deviation is implemented with appropriate review and approval by an IRB and, when applicable, by the sponsor, then it is a change in research as allowed under the regulations at 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4) rather than a protocol deviation. If it is implemented without such review and approval, then it is an intentional protocol deviation.

VI. Recommendations

Consistent with section I above, SACHRP recommends that OHRP and FDA issue a joint guidance, or if that is not feasible consistent guidance, on the procedures for handling protocol deviations. The guidance should ensure the adequate protection of subject safety and integrity of the study while taking into account the burden on investigators and IRBs. The following points should be addressed:

1. The guidance should reinforce the responsibility of investigators and research staff to follow the written protocol as provided by the sponsor and approved by the IRB. Strict adherence to the protocol is more likely to protect human subjects and preserve the integrity of the data and research.

2. The guidance should encourage sponsors and investigators to develop protocols that include flexibility in research methods where possible without adversely affecting subject safety or science. Flexibility that is built into the protocol will reduce the number of changes that have to be reviewed by the IRB and should reduce the number of incidents of deviations and non-compliance by investigators.

3. The guidance should require that permanent changes to protocols be submitted to the IRB as changes to previously approved research for review and approval prior to initiation. This recommendation is consistent with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4). If a modification is minor, it may be reviewed by the expedited procedure or the convened IRB. When applicable, such changes should also have prior sponsor review and approval. Permanent changes to the protocol that are administrative in nature and have no material effect on the regulatory criteria for approval of research, such as a change in telephone number, may be handled outside the IRB process (i.e., by IRB staff).

This is consistent with Section E of the current OHRP "Guidance on IRB Approval of Research with Conditions," which states the following: "*Protocol corrections that are only administrative in nature (e.g., correction of typographical and spelling errors in the protocol) would not need additional IRB review because OHRP does not consider such corrections to be changes to the research.*"

4. The guidance should also address one-time intentional protocol deviations that are not intended as a permanent change to the protocol. The guidance should state that these deviations are changes to the research that require IRB review and approval, and when applicable approval by the sponsor, before the investigator may implement them. These deviations will commonly qualify for expedited review by the IRB. This is SACHRP's central recommendation, as noted above.

5. The guidance should address the administrative procedures and regulatory status when investigators implement one-time intentional protocol deviations without IRB approval. The guidance should address whether this always constitutes non-compliance with the IRB regulations that must be reported to the IRB. The IRB should determine whether reported intentional protocol deviations affect the criteria for approval of research found at 45 CFR §46.111 and 21 CFR §56.111, and evaluate such deviations according to the IRB's policies and procedures for handling non-compliance and considering whether the deviation constitutes an unanticipated problem involving risks to subjects or others. For research under FDA regulations, the sponsor should also be notified and evaluate the deviation according the sponsor's policies and procedures for handling non-compliance. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events."

6. The guidance should explicitly distinguish the three types of protocol deviations described in Sections II-IV above. The guidance should also distinguish the three types of deviations from deviations to eliminate apparent immediate hazards and from IRB-approved changes in research.

7. The guidance should specifically address administrative procedures and regulatory status of *deviations from the protocol that are identified before they occur, but cannot be prevented.* The guidance should also contrast those procedures and regulatory status from the procedures and regulatory status for intentional protocol deviations. The investigator should evaluate whether these types of protocol deviations are an unanticipated problem involving risks to subjects or others that needs to be promptly reported to the IRB. Because these protocol deviations are identified before they occur but cannot be prevented, it will usually not be appropriate to submit these deviations to the IRB for prior review and approval as a change in research for two reasons. First, the IRB may decide not to approve the deviation, and second, the IRB may not be able to review the reported deviation prior to its occurrence. Both of these circumstances leave the investigator in the position of not having IRB approval to implement a deviation that the investigator cannot prevent. For research under FDA regulations, the investigator

should also inform the sponsor immediately, and the sponsor should also evaluate these protocol deviations as part of its monitoring duties, and take any necessary actions. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events."

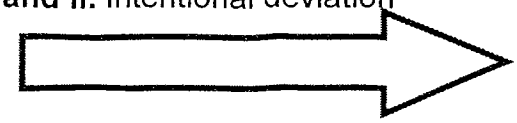
8. The guidance should specifically address administrative procedures and regulatory status of *deviations from the protocol that are discovered after they occur*. The guidance should also contrast those procedures and regulatory status from the procedures and regulatory status for intentional protocol deviations. For research under FDA regulations, the sponsor should also evaluate these protocol deviations as part of its monitoring duties and take any necessary actions. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events." It will be particularly important for the agencies to balance the burden on investigators and IRBs versus the protection of subject safety and scientific integrity when considering this issue.

9. The guidance should state that IRBs need written policies and procedures addressing the three types of protocol deviations described in Sections II through IV above. The guidance should highlight any areas where IRBs may exert flexibility in defining and determining which changes must be reported to them. For purposes of clarity, the guidance should also explicitly distinguish the two types of protocol deviations outlined in Section V above.

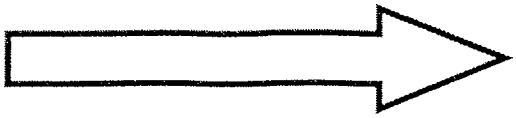
10. SACHRP recognizes that many institutions and IRBs currently do not have policies and procedures in place for reporting and/or handling the three types of protocol deviations described above. The issuance of guidance that only addresses points #3 - #9 above is likely to significantly increase the burden on IRBs. Thus, it is important that there is appropriate emphasis placed on points #1 and #2 above, both in guidance for IRBs, education for investigators, and through dissemination of best practices. For example, it would be extremely helpful to the research community for FDA and OHRP to each identify and publish, in a consistent manner, examples of how to incorporate flexibility into protocols, education programs that help increase compliance of investigators, and models IRBs can use to manage protocol deviations.

Appendix I

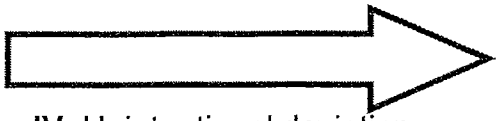
I and II. Intentional deviation



III. Unintentional deviation that can't be prevented

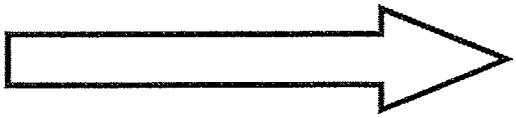


X EVENT

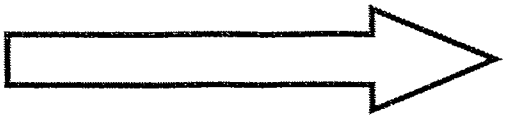


IV. Unintentional deviation discovered after the fact

V. Intentional deviation to prevent harm



V. Traditional change in research, with changes to written documents



Axis: time

Appendix II

Background - Existing Regulations and Guidance

The HHS and FDA regulations are inconsistent in addressing protocol deviations. Even among the various FDA regulations there are inconsistencies. FDA regulations and ICH-GCP requirements are inconsistent. These inconsistencies leave IRBs, sponsors, and investigators with no clear direction on how to handle protocol deviations. The HHS regulations only use the term "changes in a research activity," and state that the only changes that do not need prior IRB review are those that are "necessary to eliminate apparent immediate hazards to the subject." The term "deviation" does not appear in the HHS regulations. OHRP has not issued any written guidance on protocol deviations or on the definition of a change in research. However, OHRP's stated position is that any deviation from a protocol is a change in research that needs prior IRB review and approval.

The FDA regulations and ICH guidance both use the term "deviation" in addition to "changes in a research activity" in various sections. However, the use is not consistent among the three sets of FDA regulations (21 CFR §56, §312, and §812); nor is it consistent between the FDA regulations and the ICH guidelines. The FDA regulations pertaining to IRBs are similar to the HHS regulations pertaining to IRBs, in that, they only address "changes in research activity." However, the ICH-GCP, adopted by FDA as guidance, uses the term "deviations," and requires that IRB procedures specify "that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s))." Unfortunately, the guidance only provides examples of minor changes that do not need prior IRB review. It does not provide examples of minor deviations that do not need prior IRB review.

The FDA regulations pertaining to investigational drugs (21 CFR §312) are similar to the FDA regulations pertaining to IRBs, in that, the regulations themselves only use the term "changes in research," but do not use the term "deviation." However, as with the FDA ICH-GCP, the guidance for investigators does use the term "deviations" in a similar fashion to the ICH guidance for IRBs. The ICH states, "The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s))." As with the ICH IRB guidance, examples of minor changes to the protocol that do not need prior IRB review are provided, but examples of minor deviations that do not need prior IRB review are not provided.

Finally, the FDA ICH guidance has a section addressing the monitoring responsibilities, which is not internally consistent in regards to deviations. In §5.18.4, among the monitor's

responsibilities is "Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations." However, §5.18.6 states that monitors should report *significant* deviations in monitoring reports: "Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance." Minor deviations are not addressed and "significant" is not defined.

The FDA device regulations (21 CFR §812) are different from the FDA IRB and drug regulations, ICH guidance, and the Common Rule, in that, they specifically describe deviations from the protocol that do not require prior IRB review, and also address the role of the sponsor and FDA in regard to these deviations. The device regulations say, "prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB [approval] in accordance with §812.35(a) also is required."

Appendix III

HHS Regulation

> §46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
> (b) … Assurances applicable to federally supported or conducted research shall at a minimum include:
> (4) Written procedures which the IRB will follow
> …
> (iii) for ensuring prompt reporting to the IRB of proposed* changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
> **This word is not in FDA regulations.*

OHRP has not issued written guidance on protocol deviations. However, OHRP's unwritten position is that all planned protocol deviations are changes in research that need prior IRB review and approval before implementation.

FDA Regulations and Guidance - IRBs

> 21 CFR §56.108 IRB functions and operations. In order to fulfill the requirements of these regulations, each IRB shall:
> (a) Follow written procedures:
> …
> (3) for ensuring prompt reporting to the IRB of changes in research activity; ...
> (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

FDA Regulations and Guidance - Drugs

> 21 CFR §312.30 Protocol amendments
>
> (b) *Changes in a protocol.* (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:
>
> (i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(*a*) The sponsor has submitted the change to FDA for its review; and

(*b*) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 56.104(c).

21 CFR §312.53 Selecting investigators and monitors.
(c) Obtaining information from the investigator. Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:
(1) A signed investigator statement (Form FDA-1572) containing:
(vii) A commitment by the investigator that, ... the investigator will promptly report to the IRB all changes in the research activity ... and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

21 CFR §312.66 Assurance of IRB review.
... The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

FDA Compliance Program Guidance Manual, Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, December 8, 2008.
Protocol deviations. A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective exception to the protocol (e.g. agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria). Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35(a)(2)), and generally

communicated to FDA. "Protocol deviation" is also used to refer to any other, unplanned, instance(s) of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. Determine whether changes to the protocol were:

iv. Documented by an amendment, dated, and maintained with the protocol;
v. Reported to the sponsor (when initiated by the clinical investigator); and
vi. Approved by the IRB and FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazard(s) to human subjects).

FDA Regulations and Guidance - Devices

21 CFR §812.35 Supplemental applications.

(a)Changes in investigational plan --(1) Changes requiring prior approval. Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under 812.30(a), and IRB approval when appropriate (see 56.110 and 56.111 of this chapter), prior to implementing a change to an investigational plan.

(2)Changes effected for emergency use. The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see 812.150(a)(4)).

(3)Changes effected with notice to FDA within 5 days. A sponsor may make certain changes without prior approval of a supplemental application under paragraph (a)(1) of this section if the sponsor determines that these changes meet the criteria described in paragraphs (a)(3)(i) and (a)(3)(ii) of this section, on the basis of credible information defined in paragraph (a)(3)(iii) of this section, and the sponsor provides notice to FDA within 5-working days of making these changes.

(i)Developmental changes. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

(ii)Changes to clinical protocol. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to changes to clinical protocols that do not affect:

(A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the

protocol;

(B) The scientific soundness of the investigational plan; or

(C) The rights, safety, or welfare of the human subjects involved in the investigation.

21 CFR §812.150 Reports.

(a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:

...

(4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical wellbeing of a subject in an emergency. ... Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with §812.35(a) also is required.

FDA Regulations and Guidance - ICH-GCP (E6)
ICH sections 1.45, 3.3.7, and 4.5.2

General Principles

§1.45 Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

IRB

§3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

§3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 4.5.2).

Investigator

§4.5 Compliance with Protocol

§4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

§4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

§4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

§4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

§5.18.4 Monitor's Responsibilities

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:...

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

§5.18.6 Monitoring Report

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.

SACHRP Recommendation Regarding Oversight of Research Misconduct and Regulatory Noncompliance

Over the past few months, SACHRP, both in its own sessions and in those of its Subcommittee on Harmonization, has considered the intersection of the jurisdictions, regulatory processes, and sanctions of the Office for Human Research Protections (OHRP) and the Office of Research Integrity (ORI). As described more fully herein, SACHRP also has noted this jurisdictional and procedural intersection in light of the proposed rule of the Food and Drug Administration relating to possible falsification of data by investigators. 75 Fed. Reg. 7412 (Feb. 19, 2010). These various regulatory regimes interact in complex ways with existing institutional processes for protecting human subjects, for preserving the reputation of the respondent, and for investigating allegations of research misconduct. Most importantly, the circumstances in which human subjects research may deviate from accepted professional standards do not necessarily respect the fine-grained distinctions between noncompliance under the Common Rule, research misconduct, and violations of FDA regulations. In our deliberations in this area, SACHRP has identified some significant disharmonies between these sets of procedures that govern (or in the case of the FDA's pending proposal, would govern) noncompliance with regulatory standards relating to research with human subjects. tSACHRP asks that these issues be addressed in unified or coordinated guidance from these agencies within the Department of Health and Human Services, or, to the extent necessary, by regulatory amendments.

According to presentations made to SACHRP by ORI representatives, ORI accepts jurisdiction over matters relating to possible fabrication, falsification, or plagiarism in research funded by the Public Health Service (PHS). Of course, alleged fabrication or falsification of data, or plagiarism of previous scholarly work and data may occur in any research, not limited to research with human subjects. In identifying categories of alleged violations that would be included in its jurisdiction, ORI historically has deferred to OHRP in certain matters relating to human subject research, consistent with OHRP's jurisdiction over possible violations of the Common Rule, 45 CFR 46. ORI has typically, for example, deferred to OHRP in relation to, among other matters, allegations of falsified or forged consent forms, failure to obtain informed consent, failure to report unanticipated adverse events, forging an investigator's signature, enrolling subjects who fail to meet eligibility criteria, and protocol deviations of other sorts. At the same time, ORI has reported that it would accept jurisdiction over allegations of substituting one research subject's record for another, changing research records to reflect desired data and results, altering subject eligibility test results, and falsifying dates on screening logs for prospective subjects.

1. Overlapping Regulatory Regimes of <u>OHRP, ORI and FDA</u>

SACHRP has presented a series of jurisdictional scenarios that would seem to illustrate the overlapping nature of noncompliance under the regulatory regimes overseen by OHRP, ORI and FDA. Among the scenarios that SACHRP has offered for discussion include:

- An investigator falsifies informed consent forms in a PHS-funded study in which informed consent has been described in detail in the research protocol approved by the IRB, but study subjects were otherwise treated appropriately. In publication, the human subjects section inaccurately describes the elaborate informed consent process that was described in the protocol and approved by the IRB, but that was not followed by the investigator. The IRB discovers this serious human subject research regulatory deviation, and requires that the investigator not use the collected data. The study, paid for with significant federal grant funds, is now worthless. There has been falsification of documents, with significant harm to research integrity and a waste of federal funds, all caused by significant deviations from an IRB-approved protocol.

- To achieve statistically significant results in an NIH-funded study, an investigator fabricates research data on 50 subjects, and reports enrollment as 100. Only 50 subjects actually enrolled and completed a complicated, lengthy protocol, and the protocol had no direct benefit to the subjects. The investigator combines the fabricated data on 50 fictitious subjects with actual data on the 50 true subjects, and publishes the results, which are then also used to support an FDA submission, This represents fabrication of data, deviation from an IRB-approved protocol that is so significant that it has destroyed the integrity of the study, and submission of false information to the FDA. This research misconduct would also seem to represent a serious violation of standards relating to human subjects research and of FDA regulations..
  Further, if subsequent studies (for example, the progression to phase II o r phase III studies) were premised on inaccurate results in this study, then subjects in the later studies would have been put at unjustifiable risk; the gravity of protocol deviations in this study would thus have been compounded by later reliance on study results, with subjects directly endangered.

- An investigator falsifies eligibility criteria information on enrollment forms for subjects, so that a full complement of subjects can be enrolled quickly. The study is conducted with multiple subjects whose eligibility criteria/enrollment forms were falsified. A research misconduct inquiry process, undertaken under ORI requirements, reveals this. Thereafter, disclosure is made to the IRB, leading to an IRB finding that multiple subjects who were actually ineligible for the study were subjected to serious and harmful research interventions. This incident of research misconduct also should be viewed as a violation of human subjects research standards under 45 CFR 46.

- In a study partially funded by NIH, an investigator fails to report serious and unexpected adverse events that are directly related to the test article. These serious and unexpected adverse events in turn were not reported in publications or in subsequent FDA submissions. The study publications and FDA submissions erroneously indicate, in fact, that few or no serious adverse events occurred during the study. This course of conduct by the investigator would seem to constitute FDA violations, research misconduct, and a violation of human subjects research standards.

2. Differences in Institutional Compliance with Processes, Standards and Enforcement

In such cases as those set forth above, processes for pursuing allegations of research misconduct, possible deviations from human subjects research standards, and FDA violations vary significantly.. FDA on-site enforcement actions and the relatively informal processes that may be employed by IRBs under the Common Rule tend to be much more rapid than the ORI-mandated processes of inquiry and investigation for possible research misconduct. Second, the burden of proof of violations and evidentiary standard are undefined under the Common Rule, but are designated as the "preponderance of evidence" under ORI's regulations. Third, OHRP generally enforces Common Rule standards against institutions, under the terms of their FederalWide Assurance (FWA), while ORI and FDA typically impose sanctions against individual investigators rather than research institutions, unless they also find failings in an institution's internal processes. Fourth, ORI processes stress the confidentiality of research misconduct proceedings and the need to protect an investigator's reputation, while FDA operates to enforce regulations of compelling public importance, and while Common Rule standards are much more concerned with protection of human subjects than with the peer and public perceptions of an investigator. Fifth, in order to establish research misconduct, there must be specific evidence of fabrication, falsification or plagiarism by an individual investigator, while FDA and Common Rule standards focus on violations of and deviations from standards, regardless of investigator intention and regardless of causation that is traceable to any identified individual..

Specifically, SACHRP has received comments from institutional officials whose internal compliance efforts in regard to human subjects research and research misconduct (as defined by ORI) have been vastly complicated by the differences in regulatory processes and standards, including those relating to burden of proof and confidentiality. Our research institutions appear to be disadvantaged in their compliance efforts by confusion in regard to matters that span ORI, FDA and OHRP jurisdiction, given that IRB and research misconduct proceedings typically are

triggered by a common set of events, and that one proceeding can lead rapidly to the commencement of another procedure.

Among the composite scenarios described in presentations to SACHRP by institutional officials have been the following:

- An IRB investigated a situation that arose during a parallel research misconduct proceeding, but IRB findings and penalties (suspension of an investigator from conducting human subjects research for a defined period) long preceded any conclusion reached in the research misconduct process. The IRB made its required report to OHRP, which then replied by accepting the report and, upon receipt of FOIA requests, providing the report to the public. Therefore, the human subject violations that formed an essential component of the potential research misconduct, were already determined and information about those violations publicly available, prior to the conclusion of the research misconduct process.

- In parallel proceedings, and closely related fact patterns, an IRB and a research misconduct process led to findings that noncompliance with Common Rule standards had occurred, but research misconduct allegations were not substantiated. The IRB and the research misconduct process reached different conclusions about the basic facts of what had occurred. The project was supported by a PHS grant. The institution therefore had two differing, conflicting sets of fact findings, and was confused about what to report: reporting the IRB findings to OHRP and PHS would have been consistent with OHRP and PHS requirements, but would have reflected badly on the investigator's integrity; at the same time, respecting the finding that research misconduct had not been substantiated would have preserved the investigator's reputation but would have violated required reporting to OHRP and to PHS, as grant sponsor.

- An IRB investigated fabrication of informed consent documents and related violations of eligibility criteria for enrollment, and then suspended the protocol, requiring the investigator to notify subjects of the study suspension and of the reasons for the suspension. Although the matter was referred also to the research misconduct inquiry process, subjects and co-investigators were advised of the Common Rule regulatory violations – as was OHRP in an institutional letter reporting the suspension – long before any research misconduct process had been completed. The investigator protested, suggesting that his reputation was being ruined before the confidential misconduct process had even passed the inquiry stage.

- In an attempt to preserve the required confidentiality of the research misconduct process, a research integrity official at the institution failed to disclose to the IRB an allegation of

research misconduct in an ongoing study with human subjects. At the time the allegation was received, there was no indication that the alleged research misconduct could be placing subjects at any increased risk of harm, but the subsequent research misconduct inquiry and investigation produced evidence that subjects had been placed at increased risk. Had the IRB known these facts (or had the IRB known enough to have initiated its own investigation), the study would likely have been suspended, but the IRB did not learn of the research misconduct allegation until many months after it had been reported to the research integrity official. Ultimately, the investigation process resulted in a finding that research misconduct in fact had occurred; however, by that point, the study had concluded. Subjects had been exposed to risks in a discredited study.

These are only a few examples of the many ways in which applying Common Rule standards and OHRP guidelines can become enormously complex when the allegations also suggest possible research misconduct.

3. Specific Issues Requiring Clarity

Among the specific questions that SACHRP suggests merit official guidance are the following:

- Does a sufficiently credible and specific allegation of misconduct in research involving human subjects qualify as an "unanticipated problem involving risks to subjects or others or any serious or continuing noncompliance" that requires prompt reporting to OHRP?

- How should the IRB, the research integrity officer and the institutional official interact with one another about serious allegations received in which both human subjects and research misconduct issues are implicated? Given regulatory requirements of confidentiality in the research misconduct process,[1] should a research integrity officer advise the institutional official and the IRB of allegations that relate to human subjects protections, and if, so, at what point in the research misconduct process?

- When records and data have been sequestered, as required, in a research misconduct proceeding, what access should an IRB have to those materials, when they are needed for a related IRB inquiry?

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[1] See 42 CFR 93.108: "Disclosure of the identity of respondents and complainants in research misconduct proceedings is limited, to the extent possible, to those who need to know, consistent with a thorough, competent, objective and fair research misconduct proceeding, and as allowed by law."

- For OHRP reporting purposes, corrective actions, and notification to subjects, what should an IRB do if IRB determinations are made prior to or the determinations differ from final research misconduct findings on the same factual issues?

- To what extent should IRB determinations of serious noncompliance be factored into an institution's responsibility to "protect or restore" the reputation of an investigator who has been cleared of closely related research misconduct allegations?

- How should a research misconduct proceeding treat an IRB finding that alleged noncompliance with Common Rule standards was not substantiated, when the research misconduct process yields differing determinations on essentially the same evidence? Should it matter to the analysis of this question that the research misconduct process employs a specified standard of proof ("preponderance of the evidence")?

  What considerations should IRBs use in determining whether and how research subjects should be informed if falsification or fabrication of data has been identified, or if research misconduct has been conclusively determined, in a study in which the subjects participated?

  4. Investigation and Sanctions Process for Investigators Accused of Serious Violations of Human Subjects Regulations

As noted previously, OHRP generally enforces Common Rule standards against institutions, while ORI and FDA typically impose sanctions against individual investigators rather than against research institutions, unless they also find failings in an institution's internal processes. SACHRP understands that OHRP does have the authority to refer egregious cases of violations of human subjects regulations in HHS-funded research to the Secretary for consideration of enforcement actions against individual investigators, such as debarment from applying for or benefiting from HHS research funds. However, SACHRP also understands that this authority has never been exercised by OHRP. Furthermore, this enforcement pathway may not formally incorporate due process protections for investigators who are accused of serious and intentional violations of human subjects regulations.

The situation outlined here creates a serious inconsistency in how the Department addresses various ways in which individual investigators may deviate from professional standards of conducting research . On the one hand, the Department has the ability, through ORI, to sanction a PHS-funded researcher who is found, after an ORI process, to have engaged in research misconduct (i.e., fabrication, falsification or plagiarism (FFP)), and through the FDA, to sanction

an investigator who violates FDA regulations. On the other hand, it is much less obvious how the Department can, and under what circumstances the Department should, sanction an individual investigator who engages in serious violations of HHS human subjects regulations. This leads to the possibility, for example, that a PHS sponsor such as the NIH might be unaware of an investigator's history of serious and intentional violations of human subjects regulations when considering a grant application from that individual. This apparent gap is difficult to defend, may lead to subject harm, and may jeopardize public trust in the research enterprise should an example of egregious previous violations of human subjects regulations by a PHS-funded investigator come to light.

To address the gap described above, SACHRP recommends that the Department develop a mechanism for investigation of such cases, for imposition of sanctions as indicated, and for communicating the relevant findings to other affected federal agencies when an HHS-funded researcher is accused of serious violations of human subjects regulations. One option might be for OHRP and/or PHS (as a research funder) to develop a mechanism for undertaking such an investigation, for recommending appropriate sanctions, and for developing appropriate communication strategies.

5. FDA Standards and Proposed Mandatory Reporting of Suspected Falsification of Data

In developing guidance for research institutions, it would seem appropriate to include specific consideration of how FDA jurisdiction, standards, processes and enforcement may interact with those of OHRP and ORI. Specifically, SACHRP is mindful of the pending proposal by FDA for adoption of rigorous requirements that sponsors (which would include sponsor institutions) report suspicion of falsification of data in clinical investigations, nonclinical laboratory studies, and clinical studies in animals. 75 Fed. Reg. 7412 (Feb. 19, 2010). Under this proposal, a sponsor that "becomes aware of information indicating that any person has, or may have, engaged in falsification of data" in such studies would be required to report this to FDA within 45 days, so that FDA would have an "early alert to potentially serious lapses in subject protection or data integrity," 75 Fed. Reg. at 7416, and would be able to take swift action to abate any threat.

The difficulty with this approach is directly related to the substance of this letter: this "early warning" by sponsors to the FDA has significant implications for, and would interact in complex ways with, existing institutional processes for protecting human subjects, for preserving the reputation of the respondent, and for investigating allegations of research misconduct. FDA

actions, if taken quickly in response to such a report, could significantly complicate IRB actions and institutional research misconduct proceedings, in ways that are not completely clear but whose outlines are already suggested by the difficulties in reconciling OHRP with ORI processes and standards. Having a third set of standards that also could apply in these settings would yield additional complexity and confusion, unless regulations and guidance clearly indicate how all three sets of standards might be applied in a coordinated, non-disruptive way.

In light of this pending FDA proposal, the questions raised by SACHRP in this letter are timely indeed, and should be addressed before additional complexity is added to an already confusing regulatory regime. SACHRP's concerns in this regard were, in fact, voiced by multiple institutions and persons that commented on the proposal when it was originally published in the Federal Register, with many comments indicating that a strict reporting FDA standard could wreak havoc on established institutional IRB and research misconduct processes.[2]

Finally, SACHRP notes that some research projects funded by various offices and agencies within HHS may be co-supported by, and/or share professional staff and resources with, research projects funded by other agencies of the United States government. In the process of addressing the issues raised in this letter, HHS may therefore wish to consider how HHS-mandated processes and standards for research misconduct may be inconsistent with the various analogous processes and standards of these other agencies.

[2] See, e.g., *Comments of the Association of American Universities and Council on Governmental Relations on FDA Proposal for Reporting Information Regarding Falsification of Data*, May 19, 2010.