Subpart A Subcommittee
Update

Felix Gyi and Daniel Nelson

Co-Chairs

Presentation to the
Secretary's Advisory Committee on Human Research Protections (SACHRP)
August 1, 2005

Charge to the Subcommittee

- **Review and assess**
  - **All provisions of Subpart A of 45 CFR 46**
  - **Relevant OHRP guidance documents**
- **Based on this review and assessment**
  - **Develop recommendations for consideration by SACHRP in three categories:**
    - **Interpretation of specific Subpart A provisions**
    - **Development of new or modification of existing OHRP guidance**
    - **Possible revisions to Subpart A**

Based on memo to Subcommittee from E. Prentice, Chair of SACHRP, 1/14/05 and subsequent discussion by SACHRP

Charge to the Subcommittee

- **Goals**
  - **Enhance protection of human subjects**
  - **Reduce regulatory burdens that do not contribute to the protection of human subjects**
  - **Promote scientifically and ethically valid research**

Based on memo to Subcommittee from E. Prentice, Chair of SACHRP, 1/14/05 and subsequent discussion by SACHRP

Subcommittee Membership

- **Gary Chadwick, University of Rochester**
- **Bruce Gordon, University of Nebraska Medical Center**
- **Felix Gyi,* Chesapeake Research Review, Inc**
- **Isaac Hopkins, Community Research Advocate (UMDNJ)**
- **Nancy Jones, Wake Forest University**
- **Moira Keane, University of Minnesota**
- **Susan Kornetsky, Children's Hospital Boston**
- **Gigi McMillan, We Can Pediatric Brain Tumor Network**
- **Daniel Nelson,* University of North Carolina**
- **Thomas Puglisi, PriceWaterhouse Coopers → VA**
- **Lorna Rhodes, University of Washington**
- **Ada Sue Selwitz, University of Kentucky**
- **David Strauss, New York State Psychiatric Institute**

co-chairs

Subcommittee Meetings

- **January 18, 2005 via teleconference**
- **February 14, 2005 in Alexandria, VA**
- **May 20, 2005 via teleconference**
- **July 20-21, 2005 in Alexandria, VA**

- **Supplemented by too many Working Group calls and e-mails to enumerate…**

Topics for Consideration by Subpart A Subcommittee

Inaugural On-Site Meeting

- **Identification of Issues**
  - **Continuing review**
  - **Expedited review**
    - **Minimal risk?**
    - **Minor changes to previously approved research?**
    - **Contingencies from convened IRB review?**
  - **Assurances**
    - **“Engaged in research?”**
    - **Off-site research in nontraditional settings?**
  - **Multi-site research**
    - **Cooperative review mechanisms?**
  - **Recordkeeping and reporting**
  - **Investigator responsibilities**

Inaugural On-Site Meeting

- **Identification of Issues (continued…)**
  - **Informed consent**
    - **Waivers?**
  - **Exemptions**
    - **Need for continuing review?**
    - **Funding agency interpretations?**
  - **IRB review of exceptions and deviations**
  - **Vulnerable populations**
    - **Additional safeguards?**
    - **Legally authorized representatives?**
  - **Definitions (…see all the above!)**

- **NOT on the list as discrete topic…**
  - **Adverse event reporting**

Inaugural On-Site Meeting

- **Criteria for Prioritizing Issues**
  - **Importance of the problem**
  - **Ease of fixing the problem**
    - **Interpretation < Guidance < Revision**
  - **Effect on human research protections**
  - **Contribution to regulatory burden**
  - **Contribution to non-regulatory burden**

Working Groups

Continuing Review

Gary Chadwick*

Isaac Hopkins

Nancy Jones

Susan Kornetsky

David Strauss*

Expedited Review

Bruce Gordon

Moira Keane*

Gigi McMillan

Tom Puglisi*

Lorna Rhodes

Ada Sue Selwitz

* Co-Chairs

Ex Officio on both groups: M. Carome, F. Gyi, D. Nelson

Second On-Site Meeting

- **July 20-21, 2005 in Alexandria, VA**
  - **Ambitious Agenda (v.2):**
    - **Review draft reports on Expedited Review**
    - **Review draft reports on Continuing Review**
    - **Consider “Minimal Risk”**
    - **Input from federal agency representatives**

And now, a word from our Working Groups…

- **Ground Rules and Caveats**
  - **First opportunity for Subcommittee review and consensus was July 20-21**
    - **This is PRELIMINARY THINKING toward recommendations**
      - **Final Subcommittee recommendations will follow**
  - **SACHRP feedback…**
    - **is welcome!**
    - **is not too early… or too late.**
    - **can help us identify issues missed.**
  - **Do not confuse "regulatory burden reduction" with "work reduction"**
    - **Requirements or interpretations that do not add meaningful protections work against those that do**

Continuing Review

Gary Chadwick and David Strauss
Working Group Co-Chairs

History

- The requirement for continuing review is a legacy of the “Syphilis Study.”
- Continuing review (CR) of research was to prevent continuing research activities in the face of unacceptable harm, futility or technological / ethical obsolescence.
- The Belmont Report does not mention continuing review as an application of its ethical principles.

Working Assumptions

- Continuing review plays a central, often understated role in the IRB process.
- Any practices that do not promote demonstrable safety and ethical practice in research diminish overall human subject protection (resource allocation)

Two Considerations:

- What do the regulations require?
  - i.e., the “letter”
- What is the intent of the regulations?
  - i.e., the “spirit”

Regulatory Provisions

- The term “continuing review” is used six times in Subpart A of the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR 46).
- All but one of these references are concerned with requirements other than the definition of the term/procedure itself.

assurances 103(b), 103(b)(4), 103(d); IRB member COI 107(e); and record keeping 115(e)

Where's the Beef?

- Only §109(e) addresses the CR process and says, in its entirety:

  "An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research."

Regulatory Requirements

- the only regulatory requirement is that research be reviewed at least yearly*

- there is no regulatory direction about what the “review” must entail.

* IRB observation is permissive, not mandatory

DHEW 1981 Preamble

Preamble states:

"The precise procedure adopted by the IRB for continuing review … should be left to the discretion of the IRB."

(FR vol 46 no.16, pg. 8378)

DHEW 1981 Preamble

Preamble states:

"The precise procedure adopted by the IRB for continuing review without unnecessarily hindering research should be left to the discretion of the IRB."

(FR vol 46 no.16, pg. 8378)

1981 Preamble Conclusions

1. The procedures adopted by the IRB for continuing review should be left to the discretion of the IRB
   (i.e., not fixed by the Department)
2. What ever procedures are used, they should not needlessly hinder research

DHEW 1981 Preamble (next sent.)

- "Reporting requirements may vary from a simple annual notification in the case of research involving little or no risk, to more frequent reporting [or for] clinical trials, the IRB may require a special mechanism to carry out data and safety monitoring functions."

  (FR vol 46 no.16, pg. 8378)

How have we done in 25 years?

- Do we have / use a simple annual “notification” in the case of research involving little or no risk?

- For clinical trials, does the IRB require a special mechanism (DMC) to carry out data and safety monitoring functions – or is this duty placed on the IRB itself?

FDA Guidance Documents

Information Sheets – Guidance for IRBs and Clinical Investigators.

"Continuing Review After Study Approval."

"the FDA continuing review regulations outline minimum requirements; they do not provide specific instructions to IRBs on how to set up their own rules for continuing review within the framework of the regulations."

FDA Guidance Documents

Information Sheets – Guidance for IRBs and Clinical Investigators.

"Continuing Review After Study Approval."

"Therefore, the regulations allow institutions or IRBs to impose greater and more detailed standards of protection for human subjects than those specified by the regulations and permit each IRB to develop procedures appropriate to its needs."

HHS Guidance Documents

Guidance on Continuing Review (July 11, 2002)

"Continuing review of research must be substantive and meaningful."

"HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review."

HHS Guidance Documents

Guidance on Continuing Review (July 11, 2002)

For research not eligible for expedited review, "at least one member of the IRB (i.e., a primary reviewer) should receive a copy of the complete protocol including any modifications previously approved by the IRB"

"All IRB members should at least receive and review a protocol summary and a status report on the progress of the research"

Progress Reports

- the number of subjects accrued;
- a summary of adverse events and any unanticipated problems involving risks to subjects or others, any withdrawal of subjects from the research or complaints about the research since the last IRB review;
- any relevant multi-center trial reports;
- a summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review;
- any other relevant information, especially information about risks associated with the research;
- a copy of the current informed consent document and any newly proposed consent document.”

HHS Guidance Documents

Guidance on Continuing Review (July 11, 2002)

"The minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB." (i.e., no "block" votes)

"Continuing review of research by the IRB should include consideration of adverse events, interim findings, and any recent literature that may be relevant to the research."

HHS Guidance Documents

"IRBs conducting continuing review of research may rely on a current statement from the DSMB or sponsor indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. The IRB must still receive and review reports of local, on-site adverse events and unanticipated problems involving risks to subjects or others and any other information needed to ensure that its continuing review is substantive and meaningful."

HHS Guidance Documents

Guidance on Continuing Review (July 11, 2002)

"The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur on or before the date when IRB approval expires."

HHS Guidance Documents

Guidance on Continuing Review (July 11, 2002)

"When continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur."

Initial Subcommittee Questions

1. When can continuing review stop?
2. Can continuing review appropriately be conducted less often than once per year?
3. Should categories 8 and 9 be expanded?
4. What is the IRB role in literature searches?
5. How should exempt research be handled?
6. Can existing guidance be consolidated?
7. What is review of “unanticipated problems” and “adverse event reports?”

More Workgroup Questions

1. What is the proper interface with DMCs?
2. Is resubmit-as-new a best practice?
3. Does guidance on setting the date of CR need to be changed? How should temporary lapses in approval be handled?
4. What does “verification” mean? 46.103(b)(4)(ii)
5. What types of study monitoring / oversight are appropriate and reasonable?
6. Does CR need to be kept on the same board?
7. What documents must IRB members review?

1. When can continuing review stop? Must it continue as long as identifying data exist, or is there a point where the IRB can close it?

- The regulations do not address this issue, and only state “an IRB shall conduct continuing review of research…not less than once per year” (§46.109(e)). While there is no written guidance from OHRP on when a research study ends, that Office has for some years held that as long as an investigator is controlling identifiable data, then continuing review must be conducted at least annually.

1. When can continuing review stop? Must it continue as long as identifying data exist, or is there a point where the IRB can close it?

- HHS and FDA have different definitions for the term “human subject research”
- FDA defines human subject research as the use of a test article with patients or controls, i.e., a “clinical trial” (21CFR50.3(c and g))
- HHS includes the concept of private information in addition to intervention, i.e., the “non-corporeal” subject (45CFR46.102(d and e))

1. When can continuing review stop? Must it continue as long as identifying data exist, or is there a point where the IRB can close it?

- Example: cooperative oncology studies sponsored by NIH remain “open” solely to collect survival data.
- The only potential risk is breach of confidentiality, and with the typical safeguards in place, the risk is very low. (low probability)
- The application of §46.111 to low risk research adds no value to human subject protection and is not a reasonable requirement.

1. When can continuing review stop? Must it continue as long as identifying data exist, or is there a point where the IRB can close it?

- Revision of existing guidance would address.
- Guidance on when IRB review may stop is complicated by the difficulty of defining when a study ends, but the most tenable definition is that a study ends when all interventions are over and/or the data collection is complete at the research site for which the IRB has oversight.
- This is consistent with the FDA definition.

2. Are there circumstances where continuing review can appropriately be conducted less often than once per year?

- No explanation for selection of the one-year.
- For minimal risk research, the requirement for yearly review is neither related to, nor "appropriate to the degree of risk."
- Only regulatory change would permit IRBs to set a longer review interval.

2. Are there circumstances where continuing review can appropriately be conducted less often than once per year?

- While there is no regulatory basis for the current content of the continuing review process itself, both HHS and FDA have pointed IRBs to §111
- Limits the flexibility of IRBs to employ appropriate procedures and criteria for ongoing review.
- Exceeds the original intent of the regulations.

2. Are there circumstances where continuing review can appropriately be conducted less often than once per year?

- Seek comments regarding changing §109(e) to allow IRBs latitude in setting review dates beyond one year for minimal risk studies, and potentially for other types of studies.
- Seek comments on the regulatory application of §111 to continuing review, i.e., permitting IRBs to develop, within their written procedures, policies and procedures for the selective application of §111 to all CR.

3. Should categories 8 and 9 from the expedited review list (Nov 1998) be expanded or clarified?

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis.

3. Should categories 8 and 9 from the expedited review list (Nov 1998) be expanded or clarified?

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

3. Should categories 8 and 9 from the expedited review list (Nov 1998) be expanded or clarified?

- Activities in these categories can be of such low risk that even expedited continuing review procedures do not meaningfully add to human subject protection.
- The “exempt categories” in the regulations recognize that not all research activities require the protection provided by IRB review or informed consent.

3. Should categories 8 and 9 from the expedited review list (Nov 1998) be expanded or clarified?

- Category 9 promotes flexibility in continuing review based upon study risk
  (all “minimal risk” studies are eligible).
- For minimal risk activities that are “not on the list,” however, the initial review must still be conducted at a convened meeting.
  (burden issue for expedited review)

3. Should categories 8 and 9 from the expedited review list (Nov 1998) be expanded or clarified?

- Expedited review category 8b should be interpreted so that expedited continuing review is permitted if no additional risks have been identified at any sites and no subjects have been enrolled since the prior review and none are currently enrolled at the IRB's research site since the preceding review (v. "ever").

4. What is the role of the IRB in literature searches at continuing review?

- The regulations do not state or even suggest that the IRB is required to perform or validate a review of the literature. Reviewing the literature is a scientific activity and as such is the responsibility of the investigator – the IRB receives the results of the review.

5. How should exempt research be handled at continuing review?

- 45 CFR 46.101(b)(1)-(6) describes human subjects research activities to which the regulations do not apply.
- Therefore, there is no requirement for “initial” IRB review or for “continuing” review as defined in Subpart A.

5. How should exempt research be handled at continuing review?

- OHRP should take steps to ensure that its caution about investigator self determination of exemptions is not intended to imply that the IRB has any responsibility for oversight of these exempt activities.
- Unnecessary review diminishes the quality of the process overall.
  (credibility and resources)

6. What is the role of review for “unanticipated problems” and “adverse event reports?”

- § 46.103(b)(5) requires “written procedures for ensuring prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others.”
- Despite having no specific regulatory basis, current HHS guidance states, “continuing review of research by the IRB should include consideration of adverse events.”

6. What is the role of review for “unanticipated problems” and “adverse event reports?”

- Because adverse event reporting / review is such a major problem and in light of the fact that other groups including OHRP, FDA and NIH are actively addressing this topic, further discussion and the development of recommendations was deferred pending progress on a solution by these other groups.

7. What is the proper interface between data monitoring committees (DMCs) and the IRB during continuing review?

- Only §111(a)(6), addresses monitoring. It states, “When appropriate, there are adequate provisions for monitoring the data collected to ensure the safety of subjects.”
- Because this affects more than just CR, the subcommittee believes further discussion and development of recommendations on DMCs should be a topic for SACHRP.

7. What is the proper interface between data monitoring committees (DMCs) and the IRB during continuing review?

- Efforts to integrate or harmonize the HHS guidance, FDA guidance and the many NIH policies on DMCs would provide a valuable opportunity to enhance substantive review.
- Defining an appropriate interface between the IRB and the DMC would reduce both investigator and IRB burden.

8. What types of oversight are appropriate and reasonable in CR? What data/information improves human subject protection?

- Both of the accrediting organizations (PHRP and AAHRRP) have standards that address continuing review. These standards list types of documents and/or information that should be provided and reviewed by the IRB. These lists essentially evolve from the HHS and FDA guidance documents.
- The focus of the accreditation standards thus reflects the federal guidance bias toward "process" rather than "substance."

8. What types of oversight are appropriate and reasonable in CR? What data/information improves human subject protection?

- Both federal regulators and voluntary accrediting organizations need to recognize and support the fact that different mechanisms can be used to achieve safe and ethical research.
- One size does not fit all

9. Some IRBs have established as institutional policy a "resubmit-as-new review," is this a best practices model?

- "Resubmit-as-new" policies represent one way to enhance the process of continuing review.
- The subcommittee generally endorsed the concept, however, only as an option for those institutions that would derive a value from the process.

9. Some IRBs have established as institutional policy a "resubmit-as-new review," is this a best practices model?

- The subcommittee believes that placing this, or any other "best practice" in federal guidance would risk it becoming a de-facto requirement for all IRBs.
- Non-regulatory educational outlets should be used to provide information on review options and best practices.

10. Does the current HHS guidance regarding setting the date of continuing review need to be changed?

- Guidance states that “in order to determine the date by which continuing review must occur, focus on the date of the convened meeting at which IRB approval occurs.”
- Given the iterative process for approvals, this guidance places an unnecessary regulatory burden on the review process and does nothing to enhance human subject protection.

10. Does the current HHS guidance regarding setting the date of continuing review need to be changed?

- This could be changed by referring to the date when the research protocol receives final approval by the IRB, not the day of the convened meeting.
- The subcommittee believes that this is fully supported by the wording of the regulations and is consistent with the authority of the IRB to extend to the Chair or experienced reviewers the full approval powers of the assembled board.

10. Does the current HHS guidance regarding setting the date of continuing review need to be changed?

- Guidance states that “OHRP recognizes the logistical advantages of keeping the IRB approval period constant from year to year throughout the life of each project. When continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur”

10. Does the current HHS guidance regarding setting the date of continuing review need to be changed?

- The need for review to be meaningful and substantive requires time for the IRB to ask questions, for the investigators to respond, and for the IRB to seek further clarification. Yet, there is an artificially short window (the "30-day rule") for granting approval. (can't start before, can't finish after)
- These two requirements work against each other and therefore, work against human subject protection.

10. Does the current HHS guidance regarding setting the date of continuing review need to be changed?

- The 30-day rule is practically and logistically problematic for IRBs and investigators.
- It can generate automatic lapses if the IRB requests clarification of the progress report during the review.
- The 30-day rule, coupled with the need for advanced submission, forces review of “stale” information.

10. Does the current HHS guidance regarding setting the date of continuing review need to be changed?

- Not allowing individual IRBs to set reasonable procedures that are appropriate to their local setting adds burden without any significant benefit.
- OHRP should revise its “30-day rule” to allow IRBs to set more flexible review schedules.

10B. How should temporary lapses in approval be handled?

Guidance states, “if an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.”

10B. How should temporary lapses in approval be handled?

- In cases where there is non-compliance and an investigator is late or delinquent in submitting for review, it is reasonable to require all study activities to stop.
- A lapse in approval because an investigator has not submitted a progress report differs from a lapse of approval when a continuing renewal has been submitted and is undergoing review by the IRB.

10B. How should temporary lapses in approval be handled?

- Asking that the IRB review separate requests to allow individual subjects to continue if it is in their best interest, is unnecessary in most instances. If it is in the interest of one subject to continue, it is likely to be in the best interests of others to continue as well.
- OHRP agrees
- Example of misinterpretation of guidance wording by sites.

10B. How should temporary lapses in approval be handled?

- New enrollments are stopped in lapsed studies in part because the consent form has expired and an assessment of risks and the adequacy of the consent information has not been made for new subjects.

10B. How should temporary lapses in approval be handled?

- Modify guidance so that when continuing review is underway, automatic study suspension is not required when the expiration date passes before review and approval are complete (i.e., IRB option).
- IRBs should specify strategies to prevent delays and unlimited or open-ended review (i.e., extensive time in the lapsed state), and specify conditions and activities that will be permitted in such circumstances.

11. What does the phrase “verification from sources other than the investigators” mean for continuing review?

- Some IRBs have established audit programs that utilize IRB staff, Chairs and members.
- Research institutions that have established a “human research protection program” have often included an audit function, usually separate from the IRB function, for investigator site audits as well as for conducting IRB operational audits.
- An audit function is a mechanism available to institutions, it is not an IRB responsibility.

11. What does the phrase “verification from sources other than the investigators” mean for continuing review?

- Establishing audit programs under this Subpart A provision is appropriate, but other techniques for “verification” exist (e.g., submission of last signed consent forms) and are useful ensuring safe and ethical research.
- Again, placing this or any other “best practices” in federal guidance would risk it becoming a de-facto requirement for all IRBs.

12. Does the CR need to be performed by the same board that made the initial approval? How do special CR IRBs impact the process?

- Current guidance says, “No.”
- Subcommittee agrees.
- This model has the potential for lack of continuity and for CR to be less substantive if multiple “initial approval” IRBs are sending all continuing reviews to a single CR-IRB, but institutions must ensure that sufficient resources and effective procedures are in place to support full compliance with regulations and protection of human subjects.

13. What documents does the IRB need to be given to conduct a continuing review?

- Current HHS guidance states “in conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research
- “At least one member of the IRB (i.e., a primary reviewer) also should receive a copy of the complete protocol including any modifications previously approved by the IRB.”

13. What documents does the IRB need to be given to conduct a continuing review?

- Controversy exists as to what constitutes a “protocol summary.”
- Guidance should be clarified to state that a “protocol summary” may or may not be a separate document
- Combinations of information sources, such as consent forms and the continuing review application may constitute a “summary.”

13. What documents does the IRB need to be given to conduct a continuing review?

- If a primary reviewer system is used, there is no added benefit of requiring that all IRB members receive an extensive summary, however, the entire protocol should be available to all members.

13. What documents does the IRB need to be given to conduct a continuing review?

- The regulations allow consultants to aid the IRB in the review of studies (§107(f)).
- The use of qualified IRB professional staff to accomplish full review of the file is a technique that some IRBs have instituted.
- This procedure can enhance human subject protections by ensuring sufficient time and attention is paid to the file review.

13. What documents does the IRB need to be given to conduct a continuing review?

- Guidance should clarify that qualified IRB staff may act as a consultant to the IRB and accomplish the review of the full study file.
- As more IRBs move to electronic application submission and review this issue will become less of a concern, because all materials will be accessible at all times.

$64M. Can existing guidance on continuing review be consolidated and integrated?

- The regulatory emphasis has become a focus on process over substance and does not support quality in review the way guidance on what is expected in the substance of the review would.

$64M. Can existing guidance on continuing review be consolidated and integrated?

- In an environment where concerns about litigation drive institutional behavior, the absence of clear and consolidated guidance results in unrealistic demands on IRBs and investigators without substantively enhancing protections for subjects. For example, guidance does not provide any threshold below which a change to an approved study, regardless of how insignificant the change is, could be exempt from review.

$64M. Can existing guidance on continuing review be consolidated and integrated?

- Guidance is not easily accessible or interpretable by any audience other than regulators or trained IRB professionals.
- This perpetuates the misperception that IRBs and not the members of research community are primarily responsible for human subjects protections.

$64M. Can existing guidance on continuing review be consolidated and integrated?

- Absence of consolidated guidance makes regulatory compliance more difficult than is necessary. IRB professionals must explore extensive “case law” in the form of FDA and OHRP determination letters, old OPRR reports, Dear Colleague letters, etc., etc. for answers to questions related to daily operations and decision-making.

$64M. Can existing guidance on continuing review be consolidated and integrated?

- The field needs simplified, unified, and practical guidance for continuing review.
- Guidance should be readable to investigators and IRB members with examples provided, standards explained, and thresholds defined.
- Guidance on the substance of review should be its focus.
- Guidance should be permissive, not proscriptive whenever possible.

Expedited Review

Moira Keane and Tom Puglisi
Working Group Co-Chairs

Regulatory Basis

Department of Health and Human Services (DHHS) regulations at 45 CFR 46.110 and Food and Drug Administration regulations at 21 CFR 56.110 provide for an expedited review procedure under which the IRB Chairperson (or one or more experienced IRB members designated by the Chairperson) may approve

(a) **research in categories appearing on a list** published in the Federal Register and found by the reviewer to involve no more than minimal risk; and

(b) **minor changes in previously approved research** during the period (of 1 year or less) for which approval is authorized.

Definition of Minimal Risk

45 CFR 46.102(i)

"Minimal Risk" means that the probability and magnitude of **harm or discomfort anticipated** in the research **are not greater** in and of themselves than those ordinarily encountered in **daily life** or during the performance of routine physical or psychological examination or tests.

IRB is specifically cautioned to think of

- risk of criminal/civil liability,
- financial risk,
- employment risk,
- stigmatization,
- insurability,
- embarrassment

in deciding if risk is truly minimal.

Rigor is the same as full review, only the number of reviewers is different

In reviewing the research, the reviewer(s) may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b). *(at a full convened IRB meeting)*

An IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Eligible for Expedited Review: (Initial Review)

1. Clinical studies: IND/IDE NOT required
2. Blood sample collection (routine methods –small amounts)
3. Prospective collection of biological samples—noninvasive means
4. Data collected though noninvasive means (routinely practiced in clinical settings)
5. Materials (data, documents, specimens etc.) have been collected or will be collected for non-research purposes
6. Collection of voice, video or digital data for research purposes
7. Individual or group behavior, surveys, interviews, oral histories

Eligible for Expedited Review: (Continuing Review)

8. Continuing review of research previously approved by the convened IRB with no further direct subject participation
9. Continuing review of research (not under IND or IDE) where the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified

Informed Consent and Expedited Review:

IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

OPRR Guidebook

Overarching Issue

Expedited review permits effective oversight of minimal risk research while permitting the majority of IRB members to focus their efforts on protecting subjects' safety, rights, and welfare in research with potentially serious risks. To the extent that expedited review can be used for minimal risk research, the limited time and resources of IRBs can be concentrated on protecting subjects facing greater levels of risk.

Questions for Consideration Expedited Review

1. **Regarding the "Conditional Approval" mechanism: Do "minor changes" identified as contingencies for approval by the convened IRB, but not explicated for simple concurrence, really need to return to a convened meeting? Can the IRB Chair or primary reviewer be given the authority to make discretionary judgments on behalf of the IRB?**
2. **Is there a need for additional categories, or more examples in existing categories, on the November 1998 expedited review list?**
3. **Is additional guidance needed concerning the interpretation of "minimal risk" in the context of expedited review?**

Questions for Consideration Expedited Review

4. **Is additional guidance needed concerning the interpretation of "minor changes" in the context of expedited review? Should examples be provided similar to those provided in some of the "minimal risk" categories?**
5. **Is there a need to define "administrative changes" to research that do not warrant even expedited review and approval.**
6. **Could IRBs be permitted to define their own "minimal risk" categories based on the nature and experience of the investigators or institutions for which they are responsible?**

Questions for Consideration Expedited Review

7. **Is there need for guidance on the appropriate use of expedited procedures for review of adverse events (AEs), serious adverse events (SAEs), safety reports, and reports of unanticipated problems involving risks to subjects or others?**
8. **Is there a need to clarify use of expedited review for minimal risk activities in research involving children or prisoners, or will this be addressed by Subpart C and D Subcommittees?**
9. **Can existing guidance on expedited review be consolidated and integrated?**

Working Group Process

- Working Group convened telephone discussions
- Some members checked other sources
  - Professional associations
  - Solicited comments (unofficially) from electronic discussion lists
  - Networking with colleagues

Preliminary Findings:

- Lack of enthusiasm for changing “the list”
- Reluctance to exercise flexibility
- Fear that to use expedited review mechanism suggests a short cut in regulatory compliance (review “lite”)
- Expedited Review may be perceived as trivializing the research proposal
- IRBs fear they will suffer regulatory sanction if decision to “expedite” is questioned
- IRBs/members are “risk averse”
- Compelling issues with Social/Behavioral/Educational Research *

Consolidation of Guidance on Expedited Review

Issue of Concern: Lack of consistency between OHRP and FDA recommendations on expedited review causes needless confusion for IRBs and investigators. Existing guidance is contained in multiple documents that are often difficult to locate on the OHRP and FDA websites.

Consolidation of Guidance on Expedited Review

Possible Recommendation:

OHRP and FDA should issue joint, consolidated guidance on expedited review. Archived or obsolete guidance should be retired and removed from the searchable sections of the web site or clearly labeled as obsolete.

Convened Review "Stipulations" for Approval

Issue of Concern: Many convened IRBs use a "stipulation" mechanism to define and permit timely verification by the IRB Chairperson (or designated IRB member) of clarifications or modifications needed for approval of proposed research.

OHRP guidance currently limits the use of "stipulation" mechanisms to situations requiring simple concurrence by the investigator to specific language dictated by the IRB. This limitation on the stipulation mechanism is needlessly restrictive and incompatible with the latitude permitted to Chairpersons in their review of other "minor changes" in research.

Convened Review
"Stipulations" for Approval

Possible Recommendation:

IRBs should be permitted to describe in their written policies and procedures "stipulation" mechanisms for defining minor changes required for approval of proposed research under which:

(a) the IRB Chairperson, or a designated IRB member-reviewer, may exercise reasonable judgment in verifying that the stipulations of the convened IRB have been satisfied; and/or

(b) a qualified IRB administrator may verify that the investigator has implemented specific language (e.g., in the protocol, informed consent document, or advertisements) dictated by the convened IRB (and requiring no subjective judgment on the part of the reviewer).

Administrative Changes to Approved Research

Issue of Concern:

IRBs often receive changes to approved research that are entirely administrative or clerical in nature and have no effect on the conduct of the research, its underlying science or methods, associated risks and benefits, or the potential willingness of subjects to continue participation. The current requirement for approval of such changes by the IRB Chairperson or a designated IRB member-reviewer does not contribute meaningfully to the protection of human subjects and actually reduces such protection by wasting the limited time that IRB members have available for substantive review and oversight activities.

Possible Recommendation:

IRBs should be permitted to define in their written policies and procedures changes to approved research that can be implemented by qualified IRB staff.

Such changes would be limited to those that are entirely administrative or clerical in nature and have no effect on the conduct of the research, its underlying science or methods, associated risks and benefits, or the potential willingness of subjects to continue participation (e.g., correction of clerical or typographical errors; changes to telephone numbers, addresses, and other contact information; renumbering of pages or sections without changes in content; other changes, as defined in written IRB policies and procedures).

Review of Activities Not Involving Human Subject Research

Issue of Concern:

A lack of understanding about the regulatory definitions of “research” and “human subject” result in IRB review of activities that do not constitute human subject research.

Review of such activities

(i) deprives IRB members of valuable and limited time that could more productively be applied to the review and oversight of serious risks in research for which the IRB is clearly responsible;

(ii) generates considerable resistance, if not hostility, from those performing the activity; and

(iii) undermines respect for the IRB process.

Review of Activities Not Involving Human Subject Research

Possible Recommendation: The definitions of “research” and “human subject” should be clarified as follows:

- **46.102(d). Research** means “a systematic investigation … designed to develop or contribute to generalizable knowledge.”
  - **Systematic** means “carried out according to a plan that allows conclusions to be drawn.”
  - **Designed** means “intended or with the purpose of” (at least in part). Intention or purpose can be established either by the investigator’s expressed intent or the investigator’s use of the information or conclusions resulting from the investigation.
  - **Generalizable knowledge** means “information represented as applicable to persons in institutions (or other limited locations or contexts) beyond the institution (or other limited location or context) in which the information was obtained.”

46.102(f). Human subject means “a living individual about whom an investigator … conducting research obtains

(1) data through intervention or interaction with the individual, or

(2) identifiable private information …. Private information must be individually identifiable (i.e., the identity of the subject is, or may readily be, ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.”

- **The identity of the subject is or may readily be ascertained by the investigator** means the “investigator can identify subjects though information that is publicly available or easily obtained.”
  - Information may be deemed non-identifiable where investigators provide a signed attestation that they will neither attempt to identify subjects nor knowingly obtain or accept information through which they may identify subjects.

- **The identity of the subject is or may readily be associated with the information** means the investigator can identify subjects though a code (or other linking information) to which the investigator has access.
  - Information may be deemed non-identifiable where investigators provide a signed attestation, countersigned by the individual or entity holding the key to any identifying code, that investigators will neither be given (nor will they accept) the key through which they may identify subjects.

Activities Not Involving Human Subject Research

Activities not encompassed within the above definitions of “research” and “human subject” do not require IRB review, approval, and oversight. Under normal circumstances, the following activities would be considered “human subject research.” However, IRB review, approval, and oversight are required on those (rare) occasions when these activities satisfy the regulatory definitions. Institutions should ensure that their policies, procedures, and educational programs provide for and require appropriate IRB oversight on such occasions.

- Journalism interviews or investigations. (Example of an exception requiring IRB review: A journalist conducts a series of interviews conducted not for news purposes but to develop a theory of personality and social development.)
- Oral history interviews. (Example of an exception requiring IRB review: An historian conducts a series of interviews to develop or confirm a generalized economic or political hypothesis or theory.)

- Interviews or observations conducted by architects for use in designing a structure. (Example of an exception requiring IRB review: Interviews conducted to develop or confirm an hypothesis or theory of architectural design.)
- Student activities conducted solely for pedagogical purposes. (Example of an exception requiring IRB review: Human subject investigations conducted by students with the intent to develop or contribute to generalizable knowledge.)

- Quality assurance, program evaluation, or “institutional research” activities intended solely to evaluate and improve an organization’s programs or services, with no application of findings outside the organization. (Example of an exception requiring IRB review: Program evaluation conducted to identify techniques that can be applied to another organization’s programs or services.)

- Feasibility studies to determine the potential utility or viability of a specific, proposed service or facility, with no application of findings to other services or facilities. (Example of an exception requiring IRB review: Feasibility studies intended to be generalized to multiple services or facilities.)

Additional Expedited Review Categories

Issue of Concern: Current expedited review categories may unnecessarily restrict the use of expedited review procedures.

Additional Expedited Review Categories

Possible Recommendation:

The Working Group identified two possibilities for expanding expedited review categories that will require additional discussion by the full Subpart A Subcommittee:

- (a) Divide the current Category 7 (for research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies) into two categories and provide additional examples. The division of this category would assist IRBs in their review of social and behavioral research.
- (b) In accordance with written policies in procedures, permit IRBs to utilize expedited review procedures for all minimal risk research.

Additional Issues Considered with No Recommendation at This Time:

- Is additional guidance needed concerning the interpretation of “minimal risk” in the context of expedited review? (Possibly. Issue deferred pending extended discussion of “minimal risk.”)

- Is there need for clarification that expedited review is generally appropriate for review of recruitment materials, advertisements, etc.? (No. Current FDA guidance is sufficient.)

Additional Issues Considered with No Recommendation at This Time:

- Can an expedited reviewer “disapprove” or “require revisions” in minor proposed changes to ongoing research without referring the matter to the convened IRB (e.g., revised, but unacceptable, recruitment materials submitted after a study has been approved and enrollment has begun)? (No. Most IRBs are currently able to handle such situations satisfactorily through negotiation between the investigator and the IRB reviewer.)
- Is there a need to clarify the use of expedited review for minimal risk activities in research involving children or prisoners or will this be addressed by the Subpart C and D Subcommittees? (No. The Subpart C and Subpart D Subcommittees will address these issues.)
- Is there need for guidance on the appropriate use of expedited procedures for review of adverse events (AEs), serious adverse events (SAEs), safety reports, and reports of unanticipated problems involving risks to subjects or others? (Yes, but this will be handled outside the Subpart A Subcommittee).

“Work in Progress”

- The “Expedited Review “ mechanism is a mainstay of IRB operations and human subject protections.
- Additional Subcommittee work is necessary to allow expedited review to “be all that it can be”.

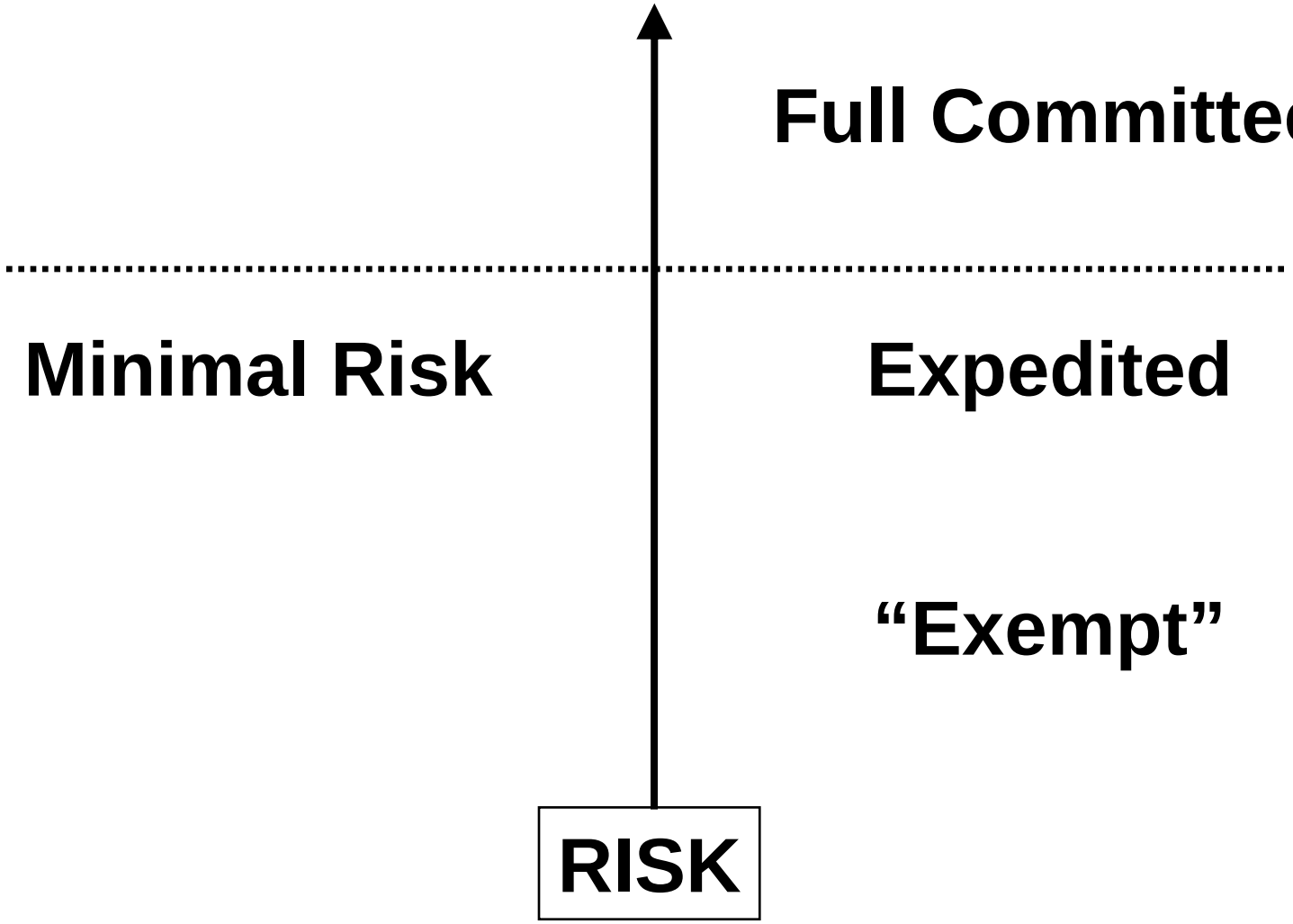
Considerations on Minimal Risk by Subpart A Subcommittee

With acknowledgements to E. Prentice…

The Risk Escalation Principle of Protection

As the risk of the research rises above the threshold of "minimal risk," there are restrictions and additional protections, particularly for vulnerable subjects.

Level of Risk Determines Level of Review



References in 45 CFR 46 to Minimal Risk

- **46.110(b)(1) Expedited review (*no more than MR*)**
- **46.116(a)(6) Explanation of any available compensation (*more than MR*)**
- **46.116(a)(6) Explanation of any available treatment (*more than MR*)**
- **46.116(d) Waiver/alteration of consent (*no more than MR*)**
- **46.117(c) Waiver of signed CF (*no more than MR*)**
- **Subpart B (*Risk not greater than MR*)**
- **Subpart C (*No more than MR*)**
- **Subpart D (*Not greater than MR; greater than MR; more than MR; minor increase over MR*)**

Definition of Minimal Risk in Subpart A

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

45 CFR 46.102(i)

HHS Clarification on the Definition of Minimal Risk

"HHS in the proposed regulations used the terminology 'healthy individuals.' In light of the public comments on this, however, HHS has reworded the final regulation to reflect its intention that the risks of harm ordinarily encountered in daily life means those risks encountered in the daily lives of the subjects of the research."

45 CFR 46
Federal Register Vol. 46 No. 16
January 26, 1981
Preamble, p. 8373

FDA Clarification on the Definition of Minimal Risk

"This definition takes into account the fact that the risks in the daily life of a patient are not the same as those of a healthy individual, and uses the risks in daily life as the standards for minimal risk."

21 CFR 56
Federal Regulations Vol. 46 No. 17
January 27, 1981
Preamble, p. 8943

Definition of Minimal Risk in Subpart C

(Research Involving Prisoners)

"Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of <u>healthy persons</u>.

45 CFR 46.303(d)

The National Commission's Definition of Minimal Risk
(Research Involving Children)

Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination of <u>healthy children.</u>

National Commission Report and Recommendations on Research Involving Children FR 43 (No. 9), January 13, 1978; p. 2085

No Definition of Minimal Risk in Subparts B&D

Failure to include a definition of minimal risk in Subparts B and D means that the definition in Subpart A applies to research involving pregnant women, fetuses, neonates, and children.

SACHRP'S Recommended Interpretation of Minimal Risk for Subpart D

The definition of "minimal risk" at 45 CFR 46.102(i) when applied to Subpart D should be interpreted as those risks encountered by normal, average, healthy children living in safe environments in daily life or during the performance of routine physical or psychological examinations or tests.

OHRP'S Clarification of Minimal Risk

OHRP has never issued official guidance regarding the definition of minimal risk on its website. However, when asked, OHRP "recommends" use of the healthy person standard when applying the provisions of Subpart A of 45 CFR 46.

Communication from M. Carome to E. Prentice 04/29/05

Subcommittee Considerations on Minimal Risk

- **Whose daily life?**
  - **Healthy person vs. subjects of research?**
    - **Does relative standard → slippery slope?**
    - **Is "healthy" or "general population" also relative?**
      - **Chapel Hill vs. Detroit vs. Baghdad?**
      - **Skydiver vs. couch potato vs. SACHRP member?**
  - **Do clarifications in 1981 Preamble set precedent?**
  - **Does 2005 SACHRP recommendation on Subpart D set precedent?**
    - **Same or different interpretation in Adults vs. Children?**
- **Does current definition imply equivalence?**
  - **Daily life = routine exams/tests?**

Subcommittee Considerations on Minimal Risk

- **Is it possible to "downgrade" greater than minimal risk to MR via minimization procedures?**
  - **Or does intrinsic risk remain a constant?**
- **Do we need to harmonize differences across regs?**
- **Biomedical vs. social & behavioral research?**
  - **Over-estimation in SBR?**
- **Would a list of examples be helpful?**
  - **MR vs. minor increase over MR vs. greater than MR**
- **All risks vs. "reasonably foreseeable?"**

Subcommittee Considerations on Minimal Risk

- **Where we ended up…**
- **What/where are the real problems with minimal risk??**
  - **Does inconsistency alone warrant fixing?**
  - **Or… is this a fix in search of a problem?**

Next Steps for Subpart A Subcommittee

- **Continuing Review and Expedited Review**
  - **Finalize Working Group Reports**
  - **Finalize Subcommittee Recommendations**
  - **Submit to SACHRP**
- **Minimal Risk**
  - **What? When? Where? How? Why?**
- **Next major topics**
  - **Exemptions**
  - **Informed Consent**

A Special Thank You

- To our Working Groups
  - Co-Chairs (Moira, Tom, David, Gary)
  - Subcommittee members
- To our colleagues at OHRP and SACHRP
  - Bernard Schwetz
  - Ernest Prentice
  - Michael Carome
  - Cathy Slatinshek
  - Kelley Booher
- To the many stakeholders providing input and suggestions