Subpart A Subcommittee (SAS)

David Borasky and Daniel Nelson

SAS Co-Chairs

Presentation to the
Secretary's Advisory Committee on Human Research Protections (SACHRP)
October 9, 2012

Outline of Today's Presentation

- Subcommittee charge and membership
- Topics for consideration at this meeting
  - Recommendations on Investigator Responsibilities
  - Recommendations on Informed Consent and Waivers of Consent
- Update on Work in Progress

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

Subpart A Subcommittee
Present Members

- Elizabeth Bankert, Dartmouth College
- David Borasky,* University of North Carolina - Chapel Hill
- Gary Chadwick, University of Rochester
- Robert Frenck, Cincinnati Children's Hospital
- Susan Kornetsky, Children's Hospital Boston
- Daniel Nelson,* University of North Carolina - Chapel Hill
- Nancy Olson, University of Mississippi
- Susan Rose, University of Southern California
- Michele Russell-Einhorn, Dana Farber Cancer Institute
- Ada Sue Selwitz, University of Kentucky
- David Strauss, New York State Psychiatric Institute

- With welcome input from
  - SACHRP members who choose to affiliate
  - Ex officio reps of Common Rule agencies

***co-chairs**

Subpart A Subcommittee
Past Members

- Ricky Bluthenthal, RAND Corporation
- Laura Beskow, Duke University
- Felix Gyi, Chesapeake Research Review, Inc
- Bruce Gordon, University of Nebraska Medical Center
- Isaac Hopkins, Community Research Advocate (UMDNJ) †
- Nancy Jones, Wake Forest University → NIH
- Moira Keane, University of Minnesota
- Gigi McMillan, We Can Pediatric Brain Tumor Network
- Ernest Prentice, University of Nebraska Medical Center
- Thomas Puglisi, PriceWaterhouse Coopers → VA
- Lorna Rhodes, University of Washington

- Not shown are multiple SACHRP members who chose to affiliate with SAS while members of parent committee

Subcommittee Meetings

- Jan 18, 2005 via teleconference
- Feb 14, 2005 in Alexandria, VA
- May 20, 2005 via telecon
- July 20-21, 2005 in Alexandria, VA
- Oct 4, 2005 via telecon
- Jan 9, 2006 via telecon
- Jan 30-31, 2006 in Rockville, MD
- May 11-12, 2006 in Gaithersburg, MD
- Sept 11, 2006 via telecon
- Oct 4, 2006 via telecon
- Feb 15-16, 2007 in Arlington, VA (+ retreat)
- Mar 9, 2007 via telecon
- May 31-June 1, 2007 in Arlington, VA
- July 16, 2007 via telecon
- Aug 16-17, 2007 in Arlington, VA
- Oct 3, 2007 via telecon
- Feb 21, 2008 in Rockville, MD
- May 15-16, 2008 in Rockville, MD
- Sept 22-23, 2008 in Rockville, MD
- Jan 26-27, 2009 in Rockville, MD
- June 8 & 30, 2009 via telecon
- July 8, 2009 via telecon
- Sept 1 & 30, 2009 via telecon
- Oct 21, 2009 via telecon
- Feb 24 & 26, 2010 via telecon
- Jun 1-2, 2010 in Rockville, MD
- Jun 30, 2010 via telecon
- Sept 27, 2010 via telecon
- Jan 26-27, 2011 in Rockville, MD
- Feb 18, 2011 via telecon
- April 18, 2011 via telecon
- May 9, 2011 via telecon
- June 13-14, 2011 in Rockville, MD
- Sept 12-13, 2011 in Rockville, MD
- Jan 13 & 25, Feb 9, 2012 via telecon
- Apr 12, 2012 via telecon
- May 3-4 in Rockville, MD
- Jun 7, 2012 via telecon
- August 6, 2012 via telecon
- Sept 5-6, 2012 in Rockville, MD

Secretarial Letters Incorporating SAS Recommendations

- **5th SACHRP letter to Secretary Leavitt → 3/14/07**
  - Recommendations approved 2005-2006
    - Continuing Review → Federal Register notice on 11/06/09
    - Expedited Review → Federal Register notice on 10/26/07
- **6th SACHRP letter to Secretary Leavitt → 6/15/07**
  - Recommendations approved March 2007
    - Required Training → Federal Register notice on 07/01/08
- **7th SACHRP letter to Secretary Leavitt → 1/31/08**
  - Recommendations approved March & July 2007
    - Waiver of Informed Consent
    - Minimal Risk → Analytical framework and examples
- **8th SACHRP letter to Secretary Leavitt → 9/18/08**
  - Recommendations approved Oct 2007, March & July 2008
    - Exemptions
    - Alternative models of IRB review
    - IRB membership rosters
    - Waiver of documentation of informed consent
    - Institutional Officials
    - American Indians and Alaska Natives
    - (Letter also addressed disaster research, and systems-level commentary)

Secretarial Letters Incorporating SAS Recommendations (continued)

- **10th SACHRP letter to Secretary Sebelius →7/15/09**
  - Recommendations approved March 2009
    - Designation of IRBs within FWA
- **11th SACHRP letter to Secretary Sebelius → 3/24/10**
  - Reaffirmation of previous rec on required education, after public RFI
- **13th SACHRP letter to Secretary Sebelius → 1/24/11**
  - FAQs on informed consent and research use of biospecimens (see below)
- **14th SACHRP letter to Secretary Sebelius → 8/5/11**
  - Parental permission, child assent, and documentation of informed consent
- **17th SACHRP letter to Secretary Sebelius → 10/13/11**
  - FAQs on biospecimen consent, revised and expanded to address HIPAA and FDA
  - Applying the Regulatory Requirements for Research Consent Forms: What Should and Should Not be Included?
- **18th SACHRP letter to Secretary Sebelius → 10/13/11**
  - SACHRP comments on federal ANPRM

Recommendations on Investigator Responsibilities

Background

- Institutions are required to provide written assurance to federal sponsors
- IRBs are required to prospectively approve non-exempt human subject research
- It is the investigator who interacts directly with the subject to obtain consent and conduct experiments
- Regulations invoke investigators predominantly in the contexts of written communications with the IRB and the informed consent process

Background

- Current Common Rule assigns responsibilities to IRBs and institutions
  - Virtually silent on role and responsibility of investigators
- FDA, ICH GCP include investigator responsibilities
  - Targets clinical/biomedical researchers

What is the problem?

- Common Rule holds institutions/IRBs accountable for the actions of investigators, even when institution/IRB has done its job
- Current requirement for research ethics training is limited in scope
  - NIH-funded research
  - Only “key personnel”
  - Once-and-done; no defined curriculum

SAS Discussions

- Previously considered by SAS → no consensus on need at that time
- Concern about adding to overall length of regulations
  - Numerous responsibilities identified
- ANPRM suggests greater level of independence from IRB oversight

SACHRP Discussion (July 2012)

- How to define *investigators*
  - All members of study team?
  - Student-researchers?
  - Principal Investigator only?

- Mechanisms of enforcement
- Harmonization issues

WRITTEN DRAFT FOR REVIEW:
Revisions to 45 CFR 46 to Address Investigator Responsibilities

Recommendations on Informed Consent and Waiver of Consent

Background

- Informed consent is a bedrock protection for human research participants, embodying the Belmont principle of respect for persons
- Regulatory default requires investigators to obtain consent of subjects prior to participation
- Regulations also anticipated scenarios where this default requirement would be inappropriate, given methodology, context or population of study → waivers

What is the problem?

- Current construct of Common Rule leads to variable understanding and application of informed consent requirements
  - Automatic "satisfaction" of all elements → contentless disclaimers
    - "Your only alternative is not to participate…."
    - Compensation for injury in MR research
  - Contributes to length and complexity
  - Failure to exercise intended flexibility
  - Difficulty in applying criteria for waiver

Prior Recommendations by SACHRP

- Waiver of Informed Consent
  - Secretarial Letter dated Jan 31, 2008
- Waiver of Written Documentation of Consent
  - Secretarial Letter dated Sept 18, 2008
- Applying the Regulatory Requirements for Research Consent Forms: What Should and Should Not be Included?
  - Secretarial Letter dated Oct 13, 2011

Effect of ANPRM?

- Prior recommendations were made within the confines of existing regulations
- Proposed reforms (ANPRM, July 2011) have opened the door to rethink current requirements and revisit prior recommendations
- ANPRM contains many concepts and elements that are not yet settled, and none are final → SAS felt obligated to work with current regs as starting point, recognizing the uncertainty

Goals of Current Proposal

- Reexamine and clarify the elements of consent
  - In particular the distribution among required and optional elements
  - Documentation of IRB determinations
- Clarify the criteria for waiver of consent

Existing Regulations: Elements of Consent

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

- *(1) to (8)*

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

- *(1) to (6)*

45 CFR 46.116 (HHS) and 21 CFR 50.25 (FDA)

Existing Regulations: Criteria for Waiver

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

- *Research involves no more than minimal risk to the subjects;*
- *Waiver or alteration will not adversely affect the rights and welfare of the subjects;*
- *Research could not practicably be carried out without the waiver or alteration; and*
- *Whenever appropriate, the subjects will be provided with additional pertinent information after participation*.

45 CFR 46.116(d), not allowed under FDA regs

SAS Discussions

- "Minimal risk" refers to foregoing definition (§46.102)
  - Remains variably understood and applied
  - See also prior recommendations
- "Rights and welfare"
  - Most subjective of four criteria
  - Legal vs. inherent rights?
  - Redundant with §116(e)?

SAS Discussions

- "Practicability" remains variably understood and applied
  - Practicability of research (in the absence of waiver) vs. practicability of obtaining consent?
- How is post-participation debriefing to be applied in biomedical research under waiver (e.g., retrospective chart reviews)?

SAS Discussions

- Are all four criteria relevant?
- Are additional criteria needed?

- Threshold too high for some partial waivers of consent
  - Difficulty of waiving selected elements works against desire to simplify and shorten consent documents

SAS Discussions

- Are waivers under some circumstances so broadly accepted and routinely granted that they should be granted peremptorily?
- With regard to the required elements, how to encourage more flexibility and less “mindless satisfaction?”

SACHRP Discussion (July 2012)

- Editing of introductory paragraphs
- Elements of consent should remain as two lists (required and optional)
  - Distribution of elements across those categories

SACHRP Discussion (July 2012)

- Waiver criteria
  - Desirability of additional guidance and/or examples?
  - Reframing of “practicability” criterion to emphasize scientific, ethical and logistical(?) justifications
  - Revert to current criteria?
- Lack of consensus across SACHRP → remanded back to SAS

WRITTEN DRAFT FOR REVIEW:
Revisions to 45 CFR 46 to Address Informed Consent and Waiver of Consent