Subpart A Subcommittee (SAS)

David Borasky and Daniel Nelson

SAS Co-Chairs

Presentation to the
Secretary's Advisory Committee on Human Research Protections (SACHRP)
July 10-11, 2013

Outline of Today's Presentation

- Subcommittee charge and membership
- Overview of prior Subcommittee work
- Work in Progress
  - Engagement of Institutions in Human Subjects Research

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
  - Included planning 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, 2012 via telecon
- 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
- Feb 20-21, 2013 in Rockville, MD
- Mar 1, 2013 via telecon
- Apr 19, 2013 via telecon
- May 22, 2013 via telecon
- June 27-28, 2013 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)
- **10th SACHRP letter to Secretary Sebelius →7/15/09**
  - Recommendations approved March 2009
    - Designation of IRBs within FWA

Secretarial Letters Incorporating SAS Recommendations (continued)

- **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
- **20th SACHRP letter to Secretary Sebelius → 1/20/2013**
  - Recommendations approved Oct 2012
    - Investigator responsibilities
    - Informed consent and waivers of informed consent
- **XXth SACHRP letter to Secretary Sebelius → PENDING**
  - Recommendations approved March 2013
    - Expedited review categories

WORK IN PROGRESS

Engagement of Institutions in Human Subjects Research

Where does the notion of "engagement" come from?

Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance…

45 CFR 46.103(a)

From Regulation to Guidance

- Beyond this single reference in the regulations, there are no requirements or indications as to what it means to be engaged or how this should be determined

Guidance

- OHRP has issued guidance to help institutions determine when they are *engaged*
  - "Guidance on Engagement of Institutions in Human Subjects Research," Oct 16, 2008
  - Which replaced…
    - "Engagement of Institutions in Research," Jan 26, 1999
    - "Engagement of Pharmaceutical Companies in HHS-Supported Research," Dec 23, 1999

Format of Current Guidance

I: Background

II: When to Use This Guidance

III: Interpretation of Engagement

(A)(1-6): Scenarios that, in general, would result in an institution being considered engaged in HSR

(B)(1-11): Scenarios that would result in an institution being considered NOT engaged in HSR

IV: IRB review considerations for cooperative research in which multiple institutions are engaged in the same non-exempt human subjects research project

OHRP Guidance on Engagement of Institutions in Human Subjects Research, Oct 2008

Why does this matter?

"When an institution is *engaged* in non-exempt human subjects research that is conducted or supported by HHS, it must satisfy HHS regulatory requirements related to holding an assurance of compliance and certifying institutional review board (IRB) review and approval."

OHRP Guidance on Engagement of Institutions in Human Subjects Research, Oct 2008

Translation

- “Engagement determines whether, when, where and how the regulations apply!”

- Guidance is amenable to clarification and change
- OHRP has asked SACHRP to consider → SAS

What is the problem?

- OHRP, institutions, IRBs and investigators all struggle with provisions
  - Institutions devote considerable resources to navigating complex scenarios, determining who is engaged, who is not, etc
- Examples in guidance are centered around the definition of HSR
  - Is the site obtaining information about subjects, obtaining consent, etc?
  - Creates potential for overlap and confusion

Who's on first?

"Regarding the relationship between the engagement of institutions in research and the terms of the FWA, we want to clarify that the Terms of Assurance apply to institutions that have already been determined to be engaged in the conduct of human subjects research. Through the FWA, the institution commits to HHS that it will comply with the requirements set forth in 45 CFR part 46, as well as the specific Terms of Assurance that identify certain requirements that the institution agrees to fulfill under the FWA. In contrast, OHRP's guidance document on engagement in research was developed to assist institutions in determining whether or not they are engaged in a particular human subjects research project. Therefore, the Terms of Assurance should not be used to determine whether an institution is engaged in a particular research project."

OHRP Correspondence on Engagement of Survey Firms, Jan 2009

Drawing the lines… is it HSR? Exempt? And where does "engagement" fit in?

NOTE: Some of the questions to determine engagement are similar to HSR, but it's not the same thing, and needs to be addressed in order

Adapted from OHRP

Issues to Consider

- Many exclusions or exceptions
  - Are direct awardees engaged, if all research activities are carried out elsewhere and prime is merely a conduit for funding?
    - Currently yes, but with case-specific exceptions
- Harmonization
  - FDA does not have equivalent assurance process
    - Applicability and enforcement focuses on investigator → 1572

Issues to Consider

- All sites are not created equal
  - Example: Multisite clinical trial with activities at some sites limited to components that could be exempt
  - For research to be exempt, the entire study must fit under one or more categories of exemption
  - In this scenario, all components are bundled together, so all sites are reviewed at the same (highest) level
  - Could the exempt components be carved out from the bundle?

Issues to Consider

- Principles of engagement
  - There should be at least one IRB reviewing non-exempt human subjects research
  - Per OHRP, not a question of avoiding or eliminating IRB review… but how much *additional* IRB review is required, for multisite research?

- Can this be accomplished without current complexity and confusion?

SAS (and SOH) Discussion

SAS Discussion

- As long as regulatory applicability hinges on engagement, no good way to abandon or ignore
- Critical decision point → dictates need for FWA and IRB review (at the engaged sites)
- Current focus on prime awardee as “always engaged” is problematic and warrants revisiting
  - Can there be allowance for differential handling of limited activities or components that occur at sub-awardee sites?

SAS Discussion (cont)

- General consensus that guidance is needed
  - Concrete examples and cases are helpful
  - Easily confused with determination if/that a given activity is “research involving human subjects”
    - Many of the questions/issues are similar
    - Need to reinforce this distinction, and the importance of making decisions in correct order

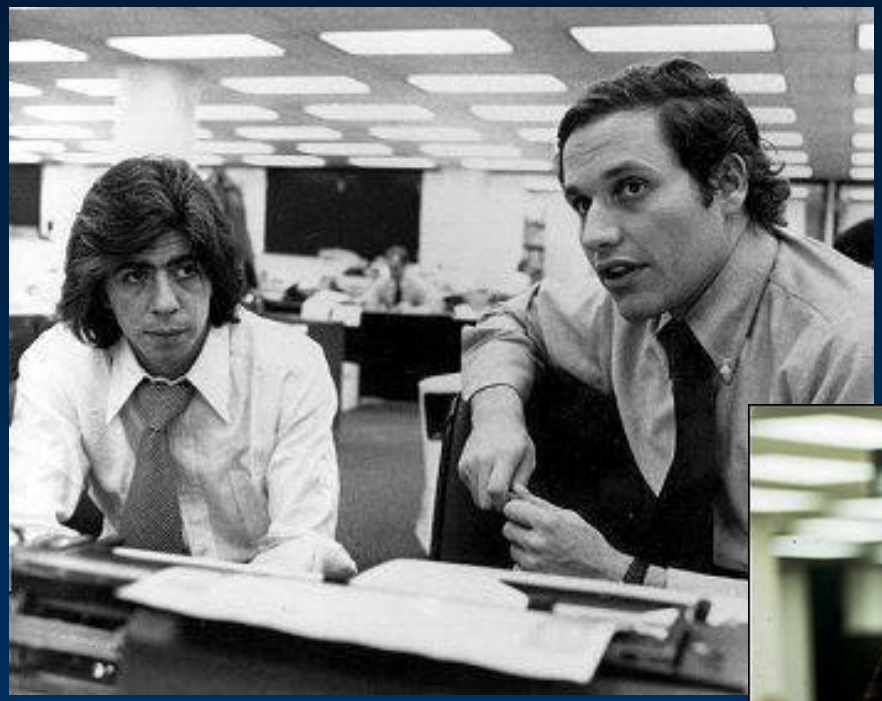
SAS Discussion (cont)

- One approach would be to review existing guidance line-by-line, revising and reordering where appropriate (e.g., as we did recently for informed consent regs under 46.116)
  - Minimal enthusiasm for this approach…
- Biggest issues/challenges arise with multisite studies → can we envision a way to pre-empt/separate those scenarios in guidance, and direct those toward review by primary/lead site??

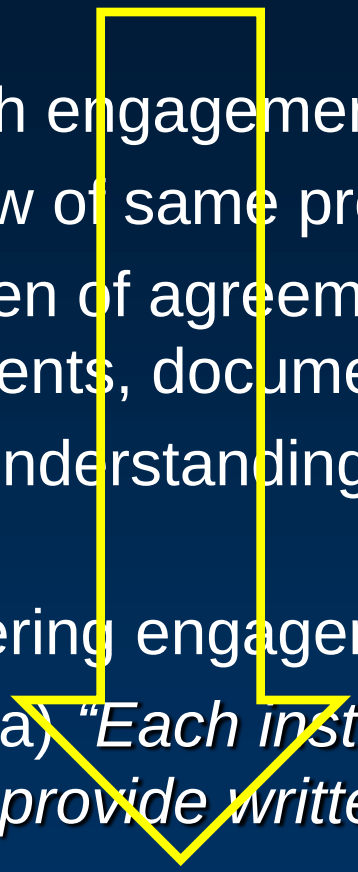
SAS Discussion (cont)

- It proves difficult to discuss without morphing into discussion on assurances
  - …since this is what drives need to define engagement
- Previous consideration of assurances, including potential to revise or reposition as other assurances are handled (e.g., as part of grant certification)
  - Tabled due to lack of interest/consensus across Common Rule agencies

“Follow the money…”



Follow the problem to the source



- What is problem with engagement?
  - Redundant review of same protocol by multiple IRBs
  - Institutional burden of agreements, collaborative review arrangements, documentation
  - Confusion over understanding, applying, interpreting "engagement"
- Why are we considering engagement in first place?
  - 45 CFR 46(103)(a) *"Each institution engaged in research… shall provide written assurance"*
- Problem starts with assurances
  - If we reposition/revise assurance mechanism → problems with engagement may become moot?

Regulatory Reference to Assurance Process

Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency *shall provide written assurance* satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads *shall accept the existence of a current assurance…*

45 CFR 46.103(a)

Statutory Basis for 45 CFR 46

SEC. 491. INSTITUTIONAL REVIEW BOARDS; ETHICS GUIDANCE PROGRAM

(a) The Secretary shall by regulation require that *each entity which applies for a grant, contract, or cooperative agreement* under this chapter for any project or program which involves the conduct of biomedical or behavioral research involving human subjects *submit in or with its application for such grant, contract, or cooperative agreement assurances satisfactory to the Secretary that it has established* (in accordance with regulations which the Secretary shall prescribe) *a board (to be known as an "Institutional Review Board") to review biomedical and behavioral research involving human subjects* conducted at or supported by such entity in order to protect the rights of the human subjects of such research.

(b)(1) The Secretary shall establish a program…

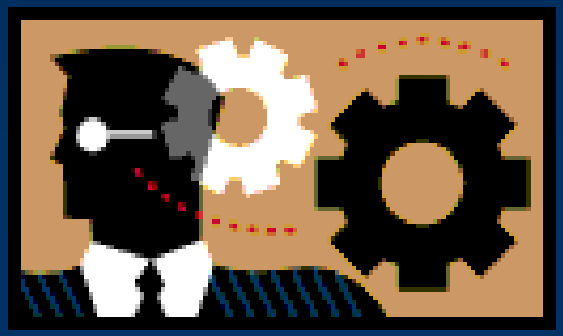
Public Health Service Act, as amended by Health Research Extension Act, Public Law 99-158, Nov 20, 1985

Think outside the box?

- There do not appear to be any regulatory or statutory restrictions that dictate HOW assurances are made
- There are other models that may present alternatives to consider
  - ORI
  - OLAW
  - NIH grants → multiple levels of “certifications, representations and assurances”

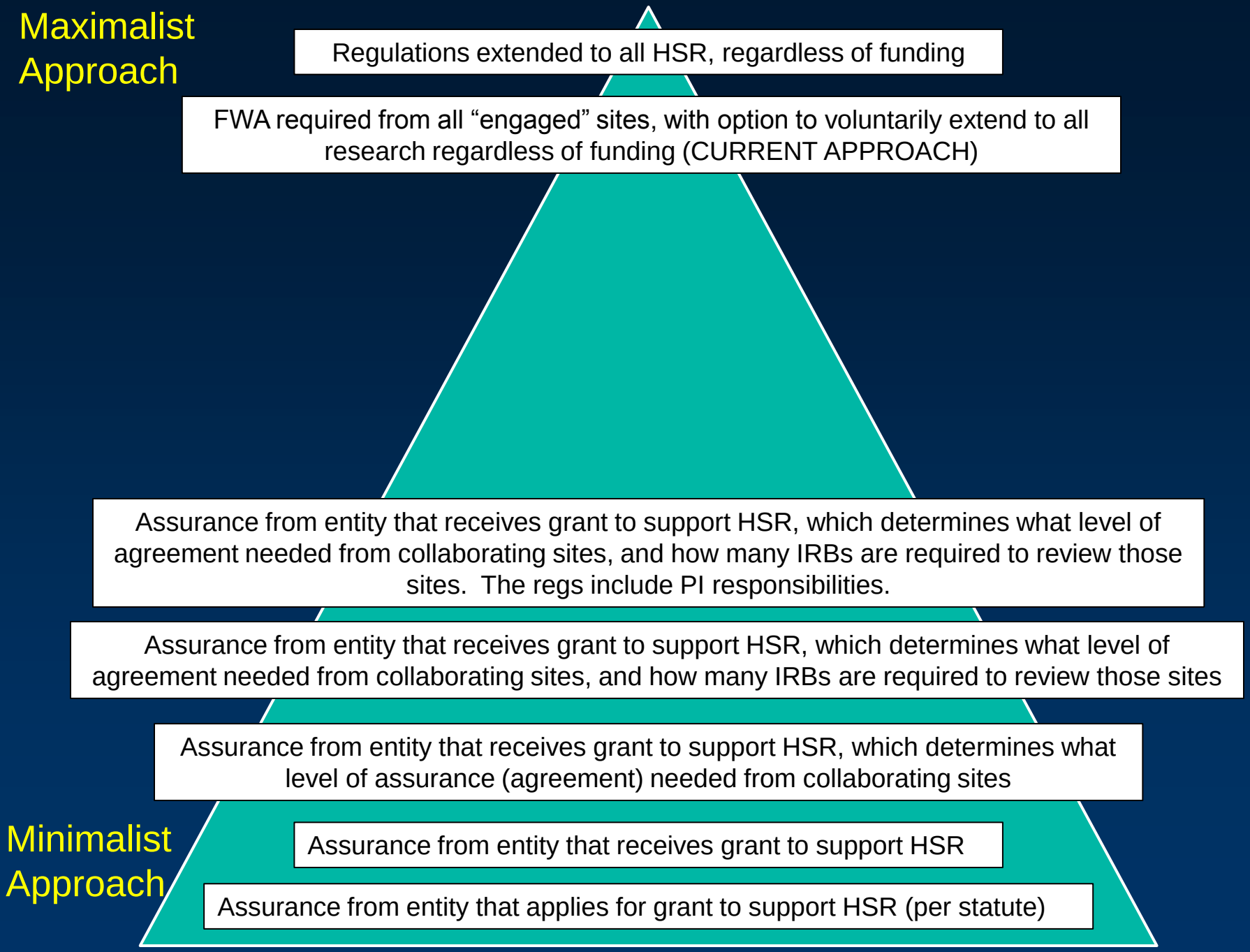
Thought Experiment

- Start over
- Forget current structure
- Rebuild from the ground up
- Add layers (requirements) as needed to accomplish goals → protect subjects



Thought Experiment

If we were starting over… who should be required to file an assurance, in what format, and when?


Maximalist Approach
Regulations extended to all HSR, regardless of funding
FWA required from all “engaged” sites, with option to voluntarily extend to all research regardless of funding (CURRENT APPROACH)
Assurance from entity that receives grant to support HSR, which determines what level of agreement needed from collaborating sites, and how many IRBs are required to review those sites. The regs include PI responsibilities.
Assurance from entity that receives grant to support HSR, which determines what level of agreement needed from collaborating sites, and how many IRBs are required to review those sites
Assurance from entity that receives grant to support HSR, which determines what level of assurance (agreement) needed from collaborating sites
Assurance from entity that receives grant to support HSR
Assurance from entity that applies for grant to support HSR (per statute)
Minimalist Approach

To be continued…

- Federal Assurance required from the entity that receives grant to support HSR
- That prime awardee then determines, at their discretion…
  - what level of agreement (MOU, etc) needed from collaborating sites
  - who serves as IRB of record
  - how many other IRBs, if any, are required to review those sites
- Comfort with this approach may increase if the Common Rule addresses include PI responsibilities, as recommended by SACHRP

Unresolved Questions That Might Add Layers

- In the ABSENCE of assurances…
  - Does OHRP have necessary authority over sites conducting research?
  - Does prime awardee (individual site) have responsibility for compliance at sub-sites?
    - If so, do they have sufficient authority via collaborative agreements?
    - Do they have resources to oversee those collaborating sites?
  - Do sites have other means to "promote the culture" for HSP?
- Are there less burdensome mechanisms to accomplish (without FWA, agreements, etc)?
- Whomever files, what is the format/content of assurance?

Unresolved Questions That Might Add Layers (continued)

- Can the Common Rule ref to “engaged” [46.103(a)] be reinterpreted (limited to funding) without regulatory change?
- Does the second ref to assurances [46.103(b)] apply to prime awardee only, or to all involved sites?
- Given the overlap (and resulting confusion) with determinations if a proposed project is research involving human subjects (HSR) → could we drop the distinction, and accept that they are actually the same?
  - That is, make the HSR determination on a site-by-site basis

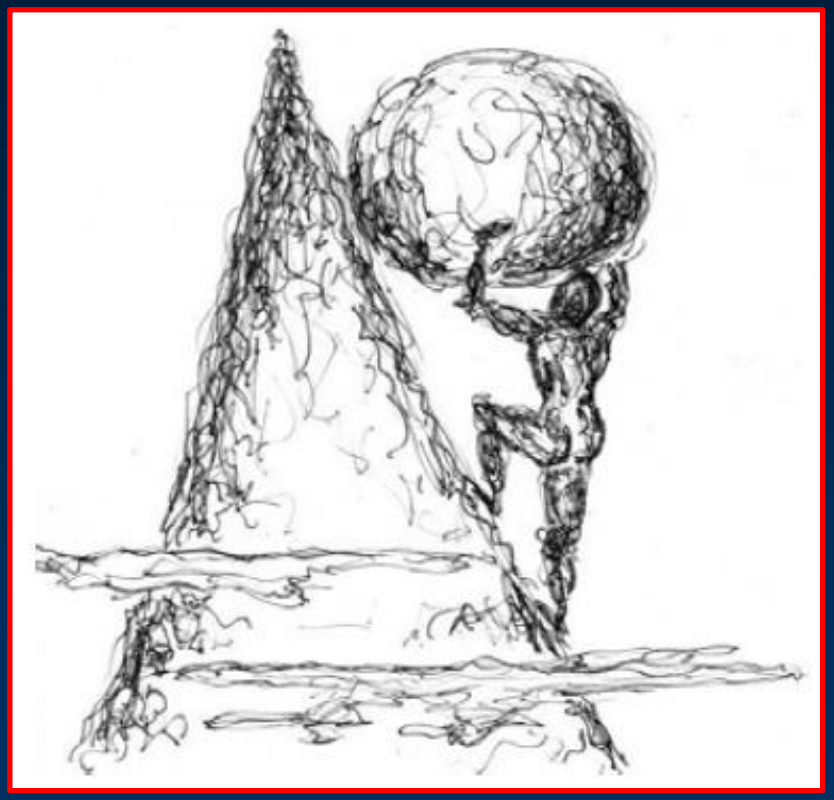
Multisite Scenario
HHS regulated

- Institution A receives the HHS grant
- Institution A must provide assurance (FWA)
  - Institution B investigators obtain consent
  - Institution C does statistical analysis
  - Institution D provides the lab services
  - Institution E releases data on subjects
  - Institution F is serving as the biorepository
  - Institution G is providing one time treatments
  - Institution H is performing intervention and measuring responses

Multisite Scenario FDA regulated

- Institution A holds the IND
- Institution A has an IRB
  - Institution B investigators obtain consent
  - Institution C does statistical analysis
  - Institution D provides the lab services
  - Institution E releases data on subjects
  - Institution F is serving as the biorepository
  - Institution G is providing one time treatments
  - Institution H is performing intervention and measuring responses

This may be the hardest SAS topic yet



We welcome (…and need!) SACHRP feedback