What’s New in GCP? SACHRP Considers Common Rule Revision; Final Action Set for December


The Secretary’s Advisory Committee on Human Research Protections (SACHRP) took its first pass at recommendations regarding revision of the Common Rule at its October meeting. The committee will make its final recommendations at its December meeting.

“The role of the advisory committee and public comment are absolutely invaluable to making sure that what we do, some two decades after the Common Rule was enacted, addresses the ever-evolving science and technologies that are available while still balancing the very real risks and respecting the autonomy of individuals to fully participate in the research process,” Wanda Jones told the committee, a day after HHS conducted a full-day town meeting on the revision.

“Yesterday’s public meeting was in many respects not surprising, but I think what most struck me was the true passion and concern that investigators, IRB members and others had,” Jones added. “First and foremost was the ultimate goal of protecting those who would participate in research without creating more barriers and also finding ways to best balance the risk of participation with the benefits.”

She added the town meeting focused on “the main issues that we knew were of highest concern, and we have open minds and open ears about this at HHS and among our federal partners.”

Jerry Menikoff, the director of HHS’ Office for Human Research Protections (OHRP), said the federal agencies “will be looking at the comments and trying to figure out the way forward. In general, [the agencies] are encouraged to be expeditious” in developing the final rules.

Joanne Less, director of FDA’s Good Clinical Practice program, noted the FDA “intends to harmonize with whatever comes out in the final rule with our own rule-making process.” She asked the committee to consider “the impact of your recommendations on FDA products because we will be looking at the comments and concerns that you raise as we develop our proposed rule.”

Subcommittee Recommendations Detailed

SACHRP spent two days examining the recommendations from its two subcommittees, which will now redraft the recommendations and have a final set ready for the December 3-4 SACHRP meeting.

“We will hear their recommendations, but SACHRP is the body that makes the recommendations to the Secretary, and so we can agree or disagree,” SACHRP chair Jeff Botkin said. “Given the nature of the [Common Rule Notice of Proposed Rule Making (NPRM)], I would like to see us have a high level of agreement on any recommendations.”

He noted that on any issues that have the committee split, “we will have to decide whether we want to present two points of view or simply not provide a recommendation. Obviously, we all have the opportunity to submit our own comments personally or through other organizations.”
Botkin added “the final rules have to be consistent with the proposals in the NPRM. We can’t come up with something entirely different and expect to see those as a possibility in the final rules. The public has to have an opportunity to comment on any set of ideas that might be incorporated into the final rule,” he said. “We can express ideas that are entirely novel, but those might well require a new NPRM in order to be incorporated within the regulations.”

“We’re not discouraging you from raising whatever issues that you want,” Menikoff added.

Botkin said one concern with the NPRM is that “some of the proposals are painted with a fairly broad brush, given the broad diversity of research and investigators.” He added the committee needed to “identify problems with clarity or inconsistency and make recommendations for clarity, even if we are supporting the particular notion, as it may be important in trying to assist those in the community.”

He added, “Two issues are potentially more complicated and controversial” — single-IRB review and biospecimen research. “The draft proposals are designed to address significant legitimate problems, but I would anticipate that there are significant concerns.”

**Single IRB Review Still a Concern**

The subcommittees’ recommendations reiterated SACHRP’s earlier stance that “mandatory single IRB review for all domestic multi-site studies is premature.”

The groups recommended strong support for the voluntary use of single IRB review and said mandatory use was “unwarranted at this time and should be removed from consideration for regulatory action.”

“Without valid data and evidence to support it, placing the mandatory use of single IRBs in the Common Rule usurps the current authorities and options of the Common Rule agencies and departments; is potentially burdensome without matching benefit; and is understudied for effectiveness, cost burden and potential unintended consequences,” the subcommittees said. “The wide room for flexibility to use combinations of review models that now exists in the Common Rule should be maintained.”

The subcommittees said they agreed with the Association of American Universities (AAU) and the Association of Public and Land-grant Universities (APLU) that the “infrastructure to support [single review] must not be an unfunded mandate... institutions will have no way to recoup the costs of setting up the infrastructure necessary to administer participating in a [single] IRB. The groups also agreed with the AAU and APLU “note of caution that mandatory single review should not result in a multitude of central IRBs... Managing multiple IRBs... would present a far greater cost and administrative burden for institutions and would seem to run counter to the intent of the policy.”

The subcommittees added mandatory use should not result in a sole-source or “too big to fail” central IRB.

“Clearly, there is a need to tread a difficult line between creating a more complex system by promulgating a unique single IRB for every multi-site study and having a single national IRB. A voluntary system seems the most likely course to achieve that balance,” the subcommittees recommended.

“If mandatory single IRB review is imposed, additional resources will be necessary to meet this requirement in the short term (e.g., IT/study tracking systems and infrastructure, institutional reporting systems, investigator training programs, monitoring mechanisms, etc.). The NPRM does not address who is to bear these not inconsiderable costs,” the subcommittees said.
“Even in the long run, major savings should not be anticipated across the research enterprise,” they added. “The most likely effect of mandatory single IRB review will be to just shift costs among parties within the system, so there will be little or no actual savings and a great possibility that institutional costs will increase due to new infrastructure needs. Supporting a national system could translate into higher government expenditures for administrative support rather than being available for conducting actual research.”

The subcommittees added, “OHRP could address some concerns about institutional liability through the development of model language for written agreements.” The agreements should include the presence of:

- Written SOPs describing how local cultural and resource-context information will be gathered, both at initial and continuing review;
- Capacity to provide for-cause site visits, as necessary;
- Written SOPs describing how the central IRB and institutions will coordinate issues, such as review by other committees (IBC, Radiation, etc.) and unique institutional policies;
- Accreditation of the Human Research Protection Program; and
- Adequate and accessible information technology (IT) infrastructure.

The subcommittees supported:

- The addition of written agreements for single-IRB review to the list of documentation requirements.
- The change to federal compliance enforcement directly with the single reviewing IRB, as proposed in the NPRM.
- OHRP and the FDA developing joint guidance that encourages greater voluntary use of cooperative review, including single-IRB review as well as combination and other models.

“Federal agencies that support single review must create mechanisms to provide incentives, including cost sharing, for implementation,” the recommendation said:

- NIH and other federal funding agencies are phasing in required single-IRB review for large multi-center clinical trials, but also allowing investigators to propose alternatives when the applicant-investigator believes it is warranted.
- Federal funding agencies are specifically asking for a justification why either local IRB review or cooperative review (including single-IRB) is appropriate. “OHRP or some lead agency could analyze such data along with input from industry experience,” groups said. “The information gained could provide support for use of single IRBs and demonstrate when such use is most advantageous.”
- NIH is funding research that evaluates the burdens and benefits to investigators, institutions and study sponsors of single mandated IRB review in studies involving more than five sites. This study should focus on the logistical and operational requirements as well as the costs of such a system.
- Federal funding agencies are providing resources for IT support for single IRB function and collect data about the operation of review mechanisms from clinical trial studies (as NIH is doing through CCTS network grants).
- Postponing compliance enforcement until the Common Rule agencies and departments have developed the tools, templates and guidance described in the NPRM and those documents, tools and products have been provided to the regulated community for input and acceptance. Upon completion of this federal process, the three-year compliance abeyance window would start to “give institutions sufficient
time to evaluate both in-house and vender systems, renegotiate contracts, determine costs and budget for expenses.”

- Regardless of whether mandated use is required or voluntary, OHRP should develop a template for written cooperative review agreements, which would include responsibilities for investigators, institutions and both single IRBs and local non-reviewing IRBs.

**Biospecimen Research Considered**

Regarding biospecimen research, the subcommittees supported the Common Rule revision’s definition of “human subject” and also agreed that the storage, maintenance or secondary research use of identified biospecimens or identified data may be exempt from the Common Rule if certain requirements are followed.

The subcommittees proposed adding a provision that the IRB, if approving waiver, should consider and require conditions to ameliorate any harm to the dignity of the subject population. The groups also suggested eliminating the proposed additional waiver criterion for research with identified biospecimens, or biospecimens (identified or de-identified) collected without notice of biospecimen and data research practices, with opt-out that the research could not be conducted with other biospecimens for which informed consent was or could be obtained. The subcommittees said that it would be “too logistically challenging and resource intensive for a researcher to fulfill due diligence requirements to survey all potentially accessible biobanks to determine whether similar, available biospecimens have associated consent.”

They also suggested revising the additional waiver criterion for research with identified biospecimens, or with biospecimens (identified or de-identified) collected without notice of biospecimen and data research practices with opt-out that requires “compelling scientific reasons” for the research use of the biospecimens.

The group said the waiver, “as described in the NPRM, [is] too restrictive and provides an unnecessary additional layer of scientific justification that may deter scientifically valid exploratory research.” The subcommittee said it should be defined as “study hypotheses and methods that are well-defined and offer promise of scientifically significant findings or results.”

In addition, “guidance should not say that waiver will be ‘rarely’ granted under this standard.”

The subcommittees also recommended:

- sanctions for the unauthorized re-identification of subjects through de-identified biospecimens or deidentified data collected for research purposes;
- transparency of the waiver of consent process for both identified data and identified biospecimens by requiring public summaries of approved waivers;
- continuing to allow secondary research on prior collections of biospecimens with identifiable information, while providing adequate human subject protections;
- deleting the requirement that secondary research use of collected biospecimens occur only after removal of any individually identifiable information associated with the biospecimens (§.101(k)(2)(ii)) and instead, grandfather identifiable biospecimens, if they were properly collected with IRB review and either informed consent or waived consent, with future uses governed by Common Rule standards in effect at the time of collection; and
- harmonizing the definition of “de-identified” with the HIPAA’s definition.
Consent Changes Generally Supported

The subcommittees generally supported the proposed changes to informed consent. However, they noted that:

- It is not clear if common template details (e.g., sponsor info) will be allowed in the main consent document.
- Consent appendices might become unmanageable spaces with an overwhelming amount of supplemental information.
- The expectations for IRB review of material in the appendices are unclear.
- If there is a consent and an appendix, it is unclear if it is a violation of IRB approval if an investigator forgets to provide participants with the appendix.

The groups noted the inclusion of three “additional” elements of consent that “address contemporary issues in research that were not anticipated in the original regulations. Positioning these as additional elements may prevent over-application by sponsors, investigators and IRBs.”

Noting the new requirement to publicly post informed consent forms “is consistent with the NPRM’s commitment to the principle of respect for persons and a desire for greater transparency with the general public,” the subcommittees said the requirement “would have the unintended effect of emphasizing the consent document over the process.”

“SAS and SOH do not support this requirement as currently written,” the recommendations said. “The potential for large additional administrative burden may not be offset by unknown public benefit [and the] rule may have negative impact on consent documents.”

The subcommittees said “a more detailed weighing of the benefit/risk trade-off of posting informed consent forms is required. Potential upside is limited, and there could be risks associated with posting them on a public website. Making forms available as teaching tools and to improve the consent process is laudable, but posting them publicly may not achieve this goal and may have the unintended consequence of making the process worse.”

The recommendation noted that consent templates are often modified at the site level and that a single template might mislead or set a false expectation for the language in the consent that was actually used at a particular investigator site. In addition, “benefits of electronic informed consent tools are negated [as] they cannot be adequately captured by the single snapshot in time that the form represents.”

They added that having the consent “in isolation to be read entirely out of context, without the benefit of knowing how the investigator conducting the process or what digital aids and tools were used to assist in participant comprehension, would be misleading. A static form presented without the benefit of a trained consent interviewer and supporting contextual materials may not meet health literacy standards and could be criticized as such when read in isolation.”

The subcommittees noted that “a likely audience for these forms will be critics and product liability attorneys, who will try to pick apart the forms in isolation of the rest of the clinical trial information and investigator/patient dialogue. Given these risks, sponsors and other researchers will seek to protect themselves by lengthening the form to make sure it covers every conceivable risk, benefit and other details that, if missing, would open the researcher up to criticism in isolation of the full study context.”

In addition, the subcommittees said it was “not clear how compliance with this rule will be monitored by regulatory agencies,...if the requirements would be limited to the main informed consent document, or if the intent is to post all of the information in the new
appendix materials, [and] what the IRB’s role would be with respect to implementation and enforcement of this requirement.”

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