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Institutional Review Boards

Consequences of Encouraging the Use of a Single IRB for Multi-Site Research: The Possibility of Less Regulatory Oversight by the OHRP

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Over the past several years, a number of Department of Health and Human Services (HHS) agencies, including the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP) and, most recently, the National Institutes of Health (NIH) have encouraged the use of a single institutional review board (IRB) for multi-site research.

The use of a single IRB for review and approval of multi-site research offers a number of potential benefits, including a source of expertise that is immune from institutional or collegial biases, unified reviews for multi-site trials and greater efficiency.[1] At the same time, the use of a single IRB for multi-site research highlights a shortcoming in the current federal regulatory schema, i.e., there is no mechanism allowing for direct OHRP regulatory oversight of external IRBs that review and approve HHS-funded or -supported multi-site non-exempt human subjects research that is not FDA regulated.[2] In order to understand this quagmire, it is best to understand the different types of IRBs currently in existence and the current 45 C.F.R. Part 46 regulatory schema.

Types of IRBs

Although there are a number of different types of IRBs in existence today, e.g., institutional IRBs, central IRBs, regional IRBs, independent IRBs, etc., all IRBs can be categorized into one of two broad categories based on the perspective of the institutions engaged in HHS-supported or -conducted non-exempt human subjects research: (a) IRBs that are internal to institutions engaged in such research; or (b) IRBs that are external to institutions engaged in such research. See also, OHRP Draft Guidance Document titled Considerations in Transferring a Previously-Approved Research Project to a New IRB or Research Institution, available at

[1] HHS Office of Inspector General (OIG), Institutional Review Boards: The Emergence of Independent Boards, June 1998 OEI-01-97-00192.

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[2] This regulatory oversight shortcoming is not applicable to FDA-regulated clinical trials because under FDA regulations at 21 C.F.R. § 56.101, the FDA has direct regulatory oversight over IRBs that review and approve clinical studies involving FDA-regulated articles. Thus, the remainder of this paper will focus on 45 C.F.R. Part 46 and its inherent shortcomings regarding this matter.

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http://www.hhs.gov/ohrp/newsroom/rfc/transferdraftdoc.html.

For the purposes of this paper, IRBs are categorized from the perspective of the institutions engaged in research because the regulations at 45 C.F.R. Part 46 apply only to institutions engaged in HHS-supported or -conducted non-exempt human subjects research; the regulations do not extend to the IRBs that engaged institutions rely upon to review and approve HHS-supported or -conducted non-exempt human subjects research, unless the IRBs are internal to the institution(s) that are engaged in HHS research. To fully understand this regulatory limitation, one must appreciate the current regulatory schema under 45 C.F.R. Part 46.

Current Regulatory Schema Under 45 C.F.R. Part 46

According to 45 C.F.R. § 46.103, each institution engaged in non-exempt human subjects research that is conducted or supported by a federal department or agency that has adopted 45 C.F.R. Part 46, must (1) hold or obtain an OHRP-approved Federalwide Assurance (FWA) [45 C.F.R. § 46.103(a)]; and (2) certify to the department or agency conducting or supporting the research that the research has been reviewed and approved by an IRB designated in the FWA and will be subject to continuing review by an IRB [45 C.F.R. § 46.103(b)].[3]

An FWA is a written document submitted by an institution (not an IRB) that is engaged in non-exempt human subjects research conducted or supported by the HHS. Through the FWA, the engaged institution commits to the HHS that it will comply with the requirements set forth in 45 C.F.R. Part 46, as well as the Terms of Assurance, when its employees or agents engage in non-exempt human subjects research conducted or supported by the HHS.

Pursuant to the OHRP Guidance on Engagement of Institutions in Human Subjects Research, available at http://www.hhs.gov/ohrp/policy/engage08.html, institutions generally are considered engaged in an HHS-conducted or -supported non-exempt human subjects research project when the involvement of their employees or agents in that project includes any of the following:

1. Institutions that receive an award through a grant, contract or cooperative agreement directly from the HHS for the non-exempt human subjects research (i.e., awardee institutions), even where all activities involving human subjects are carried out by employees or agents of another institution.
2. Institutions whose employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
3. Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment.
4. Institutions whose employees or agents interact for research purposes with any human subject of the research.
5. Institutions whose employees or agents obtain the informed consent of human subjects for the research.
6. Institutions whose employees or agents obtain for research purposes identifiable private information or identifiable biological specimens from any source for the research.

Thus, under the current regulatory schema, only those institutions whose employees or agents conduct one or more of the activities noted above are engaged in HHS-supported or -conducted non-exempt human subjects research and thereby covered by 45 C.F.R. Part 46.

Consequence

Any institution, whose employees' or agents' only involvement with an HHS-conducted or -supported non-exempt human subjects research protocol entails IRB review and approval of such research, is not subject to 45 C.F.R. Part 46 regulatory requirements because IRB review and approval of HHS-conducted or -supported non-exempt human subjects research is not an activity that causes an institution to be considered engaged in such research. Regulatory requirements under 45 C.F.R. Part 46 include, among other things, obtaining an FWA; making a commitment to the HHS that the institution will comply with the requirements set forth in 45 C.F.R. Part 46, as well as the Terms of Assurance; and agreeing to OHRP regulatory oversight.

This OHRP regulatory oversight limitation becomes apparent when one reviews the OHRP's compliance oversight history. Of note, it appears that the OHRP has never conducted an evaluation of, or issued a compliance oversight determination to, an external IRB whose only involvement with an HHS-conducted or -supported non-exempt human subjects research protocol entailed IRB review and approval of such research. See the history of OHRP compliance oversight determination letters, available at http://www.hhs.gov/ohrp/compliance/letters/index.html. The OHRP has never issued a determination letter to an external IRB because the OHRP does not have regulatory authority to do so.

To an extent, the OHRP attempted to address this regulatory oversight limitation in an April 30, 2010, correspondence regarding Use of a Centralized Institutional Review Board (IRB), available at http://www.hhs.gov/ohrp/policy/Correspondence/mcdeavitt20100430letter.html. In that letter, the OHRP states that in cases where an external central IRB is found to be responsible for any identified regulatory noncompliance with 45 C.F.R. Part 46, the OHRP will continue to clearly indicate this in its compliance determination letters and will communicate directly with the external IRB as appropriate. The OHRP then provides an example of how the OHRP addresses this issue in a recent compliance determination letter (see http://www.hhs.gov/ohrp/detrm_letrs/YR09/jun09c.pdf, section A(2), regarding the discussion of corrective actions). While the OHRP informs the research community that the OHRP will communicate directly with external IRBs when regulatory noncompliance is identified, the OHRP fails to acknowledge that it has no regu-

[3] While 45 C.F.R. Part 46 applies to all non-exempt human subjects research that is conducted or supported by any federal department or agency that has adopted 45 C.F.R. Part 46, the following discussion is limited to only HHS-conducted or supported non-exempt human subjects research because, to date, only HHS agencies have encouraged the use of a single IRB for multi-site research.

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latory authority to: (a) raise regulatory noncompliance concerns directly with external IRBs, even when these concerns are related to possible IRB noncompliance; (b) mandate that external IRBs take appropriate action to rectify identified noncompliance; or (c) take regulatory action against external IRBs should external IRBs decide not to rectify identified noncompliance, as requested by the OHRP.

Conclusion

It is imperative that any agency encouraging the use of a single IRB of record for review of multi-site research only do so after understanding the nuances of the current regulatory schema. If an HHS agency would like the OHRP to continue to have direct regulatory oversight over any single IRB selected to review and approve HHS-supported or -conducted multi-site non-exempt human subjects research, the HHS agency should require that the selected single IRB of record be internal to an institution whose employees or agents are otherwise engaged in the same HHS-supported or -conducted research protocol. See OHRP Engagement Guidance Document, Section III(A). Conversely, if an HHS agency would like to do away with direct OHRP regulatory oversight over any single IRB selected to review and approve HHS-supported or -conducted multi-site non-exempt human subjects research, the HHS should require that the selected IRB be external to any institution whose employees or agents are otherwise engaged in the same HHS-supported or -conducted research protocol.