



DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201



SEP 15 2014

TO: Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections

/s/

FROM: Suzanne Murrin
Deputy Inspector General
for Evaluation and Inspections

SUBJECT: Memorandum Report: *The Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial*, OEI-01-14-00560

This memorandum report provides information about the review by the Department of Health and Human Services (HHS) Office of Inspector General to determine whether the Office for Human Research Protections (OHRP) followed its procedures in its compliance evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT). OIG reviewed relevant SUPPORT and compliance evaluation documents and conducted interviews to assess OHRP's response to an allegation regarding the use of informed consent in SUPPORT. Specifically, OIG's objectives were:

- (1) to ensure that OHRP followed procedures and exercised reasonable discretion in the compliance evaluation of SUPPORT; and
- (2) to provide specific recommendations for how OHRP or HHS can strengthen its review, approval, and monitoring procedures if any violation is found.

We conducted this analysis in 2013 at the request of a Member of Congress, and we shared our findings with the requestor and with HHS. We are issuing this report to present our findings publicly.

SUMMARY

We found that OHRP followed its procedures and exercised discretion throughout its evaluation of SUPPORT. Generally, OHRP sees its role as educational and sees such evaluations as opportunities to strengthen human subjects protections in future research. The events following OHRP's determination in SUPPORT have raised important

questions about the protection of human subjects in research that compares treatments within the current standard of care.

BACKGROUND

OHRP

Section 491 of the Public Health Service Act (42 U.S.C. § 289) authorizes the Secretary to establish a process to respond to alleged violations of human subjects protection in research conducted or supported by HHS. The Secretary has delegated this authority to OHRP.¹ Pursuant to this authority, when OHRP receives allegations of violations it may conduct for-cause compliance evaluations.²

OHRP has developed an 11-step procedure for conducting a for-cause compliance evaluation. In general, OHRP's process involves notifying the institution and requesting that it investigate the allegation, provide a written response with supporting documents, and develop a corrective action plan if any noncompliance is revealed. OHRP evaluates the institution's response and issues a determination letter addressing the allegations of noncompliance. If OHRP identifies noncompliance with human subjects protections regulations, it can (1) require the institution to take corrective measures, such as developing a corrective action plan or improving institutional policies; (2) restrict or suspend research at the institution; and/or (3) recommend that an institution or investigator be debarred from receiving Federal funds for research.

OHRP has considerable discretion in this process. For example, OHRP is able to determine whether to conduct a for-cause compliance evaluation; how to assess the institution's investigation; whether to consult with experts; and what, if any, are appropriate corrective actions.

SUPPORT

SUPPORT was a randomized multisite study that enrolled about 1,300 premature infants between 2005 and 2009. The National Institute of Child Health and Human Development (NICHD) within the National Institutes of Health (NIH) funded SUPPORT. The University of Alabama, Birmingham (UAB) was the lead coordinating institution of the 23 sites in the study.³ Research Triangle Institute (RTI) was the data-coordinating center responsible for collecting, storing, and analyzing study data for all sites.

¹ 65 Fed. Reg. 37136–37 (June 13, 2000).

² OHRP also conducts not-for-cause evaluations in the absence of allegations or indications of noncompliance. OHRP selects institutions for not-for-cause evaluations on the basis of a range of factors, including volume of supported research, history of low-level reporting to OHRP, and geographic location.

³ Other institutions involved in SUPPORT were Case Western Reserve University, Duke University, Wake Forest University, Women and Infants Hospital of Rhode Island, Brown University, the University of Utah, the University of Cincinnati, Tufts Medical Center, the University of Texas Southwestern Medical Center, Emory University, the University of Rochester, Indiana University, Stanford University, the University of Miami, Wayne State University, the University of Iowa, Yale University, the University of California, Sharp Mary Birch Hospital for Women & Newborns, and the University of New Mexico.

One purpose of the study was to determine the appropriate levels of oxygen saturation in infants with extremely low birth weights by comparing those receiving lower levels of oxygen saturation to those receiving higher ones. Enrolled infants were randomized into two groups and maintained in one of two oxygen saturation target ranges (85–89 percent or 91–95 percent).⁴ At the time of the study, the standard of care was to treat premature infants within an oxygen saturation range of 85–95 percent. In practice, clinicians adjust oxygen saturation levels within that range according to an infant’s individual needs and characteristics.⁵

One objective of the study was to test the hypothesis that a lower target range of oxygen saturation compared to a higher range would reduce the incidence of severe retinopathy of prematurity (a disease that causes abnormal blood vessel growth in the eye, leading to blindness and other visual impairments) or death among infants with extremely low birth weights. A second objective of the study was to compare two ventilation treatments in such infants.

Allegation of Violation and OHRP’s Determination Letter. In May 2011, OHRP received an email about SUPPORT alleging that (1) the study design was unethical because some infants received “severely reduced” oxygen and (2) the researchers had not obtained informed consent. In response, OHRP conducted a for-cause compliance evaluation of SUPPORT at UAB (see Attachment: Chronology of OHRP’s Evaluation of SUPPORT). OHRP issued a determination letter to UAB in March 2013 stating that “the conduct of this study was in violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological damage and death.”

METHODOLOGY

We reviewed how OHRP conducted its for-cause compliance evaluation of SUPPORT. We assessed how OHRP followed its 11 procedural steps and how the agency exercised its discretion.

We reviewed the following documents provided by OHRP:

- the emailed allegation regarding SUPPORT;
- emails and written communication of relevant OHRP staff involved in the SUPPORT compliance evaluation, including communication among staff from OHRP, NIH, other HHS offices, UAB, and RTI;

⁴ SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, “Target Ranges of Oxygen Saturation in Extremely Preterm Infants.” *The New England Journal of Medicine*, 2010; 362: 1959–1969, May 27, 2010.

⁵ J.M. Drazen et al., “Informed Consent and SUPPORT.” *The New England Journal of Medicine*, 2013; 368: 1929–1930, May 16, 2013.

- the study documents that OHRP requested from UAB as part of its evaluation, including SUPPORT’s Data Safety Monitoring Committee (DSMC) documents and approved informed-consent documents;⁶ and
- a summary report of previous OHRP investigations or actions involving UAB.

We also reviewed the minutes for both open and closed DSMC meetings and adverse event data provided by RTI. In addition, we conducted structured interviews with OHRP and NIH staff involved with SUPPORT.

We did not review the appropriateness of OHRP’s determination or actions in its SUPPORT evaluation.

This study was conducted in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

RESULTS

We found that OHRP followed its for-cause compliance evaluation procedures, which are broadly drawn and provide the office with substantial discretion.

OHRP’s activities to ensure institutions’ compliance are not codified in Federal statute or regulations; rather, they appear in compliance procedures issued by OHRP. These procedures give OHRP considerable discretion in how it conducts such evaluations.⁷ OHRP specifies 11 steps in a for-cause compliance evaluation; we found that after receiving the allegation, OHRP followed its procedures for each step. Below, we list each step and describe the actions OHRP took and how it exercised its discretion.

Step 1: OHRP determines whether it has jurisdiction to evaluate allegations.

After receiving the emailed allegation on May 24, 2011, OHRP reviewed the published results of SUPPORT in a *New England Journal of Medicine* article referenced in the allegation and determined that the study fell within its jurisdiction.⁸ The article stated that SUPPORT was an NIH-funded study; OHRP confirmed this fact by contacting NIH. OHRP has the authority to evaluate allegations pertaining to human subject research that HHS conducts or supports.⁹ According to officials at OHRP, the agency receives between 80 and 100 allegations per year, of which 5 to 10 fall within its jurisdiction.¹⁰

⁶ A DSMC is an independent committee of experts responsible for reviewing clinical trial data on an ongoing basis to ensure the safety of study subjects and validity and integrity of the data.

⁷ OHRP, *Compliance Oversight Procedures for Evaluating Institutions*, October 14, 2009. Accessed at <http://www.hhs.gov/ohrp/compliance/evaluation/> on July 23, 2013.

⁸ SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, “Target Ranges of Oxygen Saturation in Extremely Preterm Infants.” *The New England Journal of Medicine*, 2010; 362: 1959–1969, May 27, 2010.

⁹ 42 U.S.C. § 289(b)(2); 65 Fed. Reg. .37136–37 (June 13, 2000).

¹⁰ In addition, OHRP has authority to evaluate allegations when an institution is covered by an applicable OHRP-approved Federalwide Assurance. A Federalwide Assurance is a written document that commits the institution to full compliance with HHS regulations whenever the institution is engaged in human subject research that HHS conducts or supports.

Step 2: OHRP notifies complainant as to whether it will open an evaluation.

On July 18, 2011, OHRP notified the complainant that it would be “evaluating the allegations related to informed consent/parental permission.”

Step 3: If OHRP chooses to conduct a for-cause compliance evaluation, OHRP sends an inquiry letter to the institution.

Step 4: OHRP sends copies of the inquiry letter to the principal investigator(s) involved in the research.

OHRP sent an inquiry letter to UAB and RTI on July 18, 2011, copying the principal investigator for SUPPORT along with relevant individuals at NIH, NICHD, and the Food and Drug Administration (FDA).¹¹ OHRP’s inquiry letter included all required information outlined in its procedures. It explained OHRP’s compliance procedures, described the allegations, and requested that UAB investigate and respond in writing with corrective actions if the investigation revealed a violation.

OHRP discretion in initiating the evaluation. Within 2 weeks of receiving the allegation, OHRP conducted a preliminary analysis to determine whether the allegation warranted an evaluation. OHRP first obtained from NIH the research protocol and the template for informed-consent documents. OHRP’s initial decision was that the template did not include all reasonably foreseeable risks. OHRP staff told us that OHRP chose to initiate an evaluation even though enrollment in SUPPORT had ended and therefore the element of ongoing risk to human subjects was absent. OHRP considered the evaluation to be important because NIH has increasingly funded research of similar design (i.e., involving human subjects who are assigned to receive different treatments within the current standard of care). OHRP staff reported that when they decide to initiate an evaluation, they consider primarily the level of risk to human subjects. Because each compliance evaluation requires OHRP to commit significant human resources, new evaluations may require OHRP to reprioritize ongoing or planned evaluations.

OHRP discretion in defining the scope of the evaluation. OHRP reviewed the allegation and relevant study documents and chose to focus its evaluation on one institution, one study objective, and only the informed-consent issue.

OHRP chose to focus its evaluation on the lead institution, UAB, rather than all of the institutions involved in the study. OHRP staff told us that they expected the outcomes among the multiple sites would be similar, so focusing the review on the lead institution seemed appropriate.

¹¹ OHRP staff indicated that they also included RTI because data-coordinating centers “often have access to materials that the individual sites don’t have.” OHRP later determined that RTI had limited involvement in the conduct of SUPPORT and only collected, stored, and analyzed data for SUPPORT. OHRP communicated to RTI that it need not respond.

OHRP staff also explained that they chose to focus the evaluation on one of the two research objectives of SUPPORT because the allegation referred specifically to the comparison of different oxygen saturation ranges.¹²

Lastly, OHRP focused its evaluation on the initial informed-consent document that UAB used, with the goal of determining whether that document appropriately described the research purpose and all reasonably foreseeable risks to human subjects. OHRP did not assess whether any new risks were identified throughout the trial that should have been communicated to human subjects as required by 45 CFR 46.116(b). According to OHRP staff, their concern was that known risks at the start of SUPPORT were not set out in the informed-consent document that UAB used.

Step 5: OHRP evaluates the documentation submitted by the institution in response to its inquiry letter to determine whether additional information is needed.

Step 6: OHRP engages external expert consultants as needed.

Step 7: OHRP presents any questions and concerns in additional written correspondence to the institution. OHRP can conduct interviews and onsite visits at institutions if relevant.

UAB responded to OHRP's inquiry letter on August 26, 2011, stating that it had reviewed the institutional review board (IRB) file for SUPPORT and had interviewed relevant study staff. UAB found that its informed-consent document complied with 45 CFR § 46.116(a). Specifically, UAB stated that "there were no data from evidence-based trials to indicate increased risk or benefits between the two ranges of oxygen saturations tested." It also stated that the DSMC had reviewed the study data several times and found no concerns with increased risk or benefit.

OHRP started its review of UAB's response in January 2012 when it assigned the case to a specific coordinator in its Division of Compliance Oversight. OHRP did not engage experts external to HHS in its evaluation, but it did consult experts in NIH before issuing its inquiry letter to UAB. OHRP did not conduct interviews or site visits in its evaluation of SUPPORT. OHRP requested additional information from both NICHD and UAB via email between January 2012 and April 2012. OHRP requested informed-consent documents from all SUPPORT-involved sites to conduct a comparative analysis of all the documents.¹³ OHRP also requested additional DSMC documents from UAB after receiving only some of the open meeting minutes. OHRP received no additional DSMC documents because UAB had none. OHRP also requested clarification regarding oxygen-saturation practices for premature infants at UAB at the time of the study.

OHRP discretion in prioritizing evaluations. Although OHRP received a response from UAB to its inquiry letter on August 26, 2011, it did not begin its review until

¹² The other arm of the study compared different ventilation treatments.

¹³ OHRP's analysis of all informed-consent documents found that none of the documents listed death as a risk and that two listed blindness as a risk.

January 2012. OHRP staff stated they were unable to commit resources in the interim because of ongoing evaluations and insufficient staffing. In addition, SUPPORT had completed enrollment, results had been published, and the element of ongoing risk to human subjects was absent.

OHRP discretion in engaging experts. According to OHRP staff, OHRP's review of SUPPORT was based on information included in the SUPPORT protocol and informed-consent documents written by the principal investigators themselves and no external expert was needed. OHRP staff explained that they rarely consult outside experts during an evaluation, but often contact NIH or FDA to obtain more information about specific research and related clinical practices, medical devices, or drugs. OHRP discussed handling the SUPPORT allegation in a manner similar to that of past allegations by identifying experts at NICHD who could discuss the trial and by requesting a copy of the protocol and model parental permission form. In addition, OHRP staff told us that OHRP had in-house expertise and was familiar with the science and debate regarding retinopathy and premature infants.

OHRP discretion in conducting interviews or site visits. According to OHRP staff, OHRP conducts site visits when it has concerns of systemic issues at an institution; when certain events occur, such as an unexpected death of a study subject; or when correspondence with the institution has been difficult. None of these issues were applicable in OHRP's evaluation of SUPPORT.

Step 8: On the basis of the institution's responses and any relevant information received from the complainant or other sources, OHRP issues its determination letter(s) to the institution pertaining to the allegations and the institution's program for protecting human subjects.

OHRP issued a determination letter to UAB and RTI on February 11, 2013. RTI contacted OHRP and requested that OHRP remove it from the determination letter because of its limited involvement in the trial. OHRP removed RTI from the letter and reissued it on March 7, 2013. In its determination letter, OHRP copied UAB's principal investigator on SUPPORT along with the principal investigators at each institution in the multisite trial.

OHRP's determination letter addressed in detail the specific noncompliance with Federal regulations at 45 CFR 46.11(a)(2) that require a description in the informed-consent document of any reasonably foreseeable risks and discomforts to the subject. According to OHRP staff, the determination letter included significant detail so that it could serve as a resource for the research community.

OHRP's procedures specify eight possible outcomes for evaluations, ranging from identifying no issues of noncompliance to recommending suspension and debarment of an institution or investigator. The determination letter to UAB aligns with one possible outcome that OHRP described in its procedures, i.e., a determination that the research

project as conducted was out of compliance with one or more requirements of the Federal regulations. OHRP procedures require that in such an instance the institution develop and implement corrective actions. Specifically, OHRP required UAB to provide a plan to its IRB to ensure that its approved informed-consent documents include the elements of 45 CFR § 46.116(a).

OHRP discretion in copying all institutions. OHRP conducted its evaluation at the lead institution only, but OHRP copied all institutions involved in the study to educate them regarding the issues it examined. OHRP staff told us that OHRP’s determination letters are commonly reviewed by the broader research community. OHRP staff reported that the agency’s primary purpose in overseeing federally funded research is educational rather than punitive. Furthermore, staff referenced OHRP’s common practice of limiting evaluations to one or two institutions in multisite studies and copying the others. They said that conducting one evaluation and making one determination is more efficient and achieves the same impact as the alternative—in this case, conducting 23 separate but similar evaluations.

OHRP discretion in focusing on one regulatory concern. In its original inquiry letter, OHRP listed two concerns with SUPPORT’s informed-consent documents’ not adequately addressing two basic elements required by Federal regulations: (1) a description of any reasonably foreseeable risks and discomforts and (2) an explanation of the purposes of the research. OHRP staff reported that the agency chose to focus its determination letter on the failure to describe in the informed-consent document any reasonably foreseeable risks and discomforts. The staff stated that they made this decision because they thought it would be confusing to address both concerns. OHRP staff explained that OHRP letters tend to focus on the central regulatory issue, and in this case, they believed that the issue was that human subjects were not adequately informed of the risks of participating in the study.

Step 9: If OHRP makes no determinations of noncompliance or determines that noncompliance has been adequately addressed through corrective action, OHRP concludes the evaluation and informs the institution of this final outcome in writing.

OHRP issued a determination letter, so this step was not applicable.

Step 10: OHRP informs the complainant in writing of OHRP’s determinations and any corrective actions taken by the institution upon completion of the evaluation.

At the time of our review (i.e., 2013), OHRP’s evaluation of SUPPORT was not final and OHRP had not informed the complainant of its determination.

Step 11: An institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation.

No evidence exists that UAB asked the Director of OHRP to reconsider OHRP's determination. Rather, UAB responded to OHRP's determination on March 22, 2013, with a list of corrective actions that the institution had implemented to ensure that approved informed-consent documents would include and would adequately address the basic elements of consent as required by Federal regulations. These corrective actions included a revision to UAB's template for informed-consent documents; the creation of a new protocol checklist; and a reminder to the UAB staff of the IRB that all risks must be described, even when treatment falls within the parameters of standard of care.

OHRP discretion in maintaining its determination. In mid-April 2013, NIH contacted OHRP and raised concerns regarding OHRP's determination letter. Later that month, NIH encouraged OHRP to reverse its determination. OHRP maintained its determination but suspended all compliance actions against UAB. In a followup letter to UAB on June 4, 2013, OHRP committed to providing guidance to address the appropriate way to communicate risks to human subjects enrolled in research involving different treatments within the standard of care. On August 28, 2013, HHS held a public meeting to discuss the protection of human subjects in such research.

SUMMARY OF EVENTS FOLLOWING OHRP'S DETERMINATION

In the time since OHRP issued its determination letter in March 2013, additional important events and discussion have taken place. On April 10, 2013, a consumer advocacy group brought the determination letter to the attention of the public by sending an open letter to HHS Secretary Kathleen Sebelius. The group agreed with OHRP's finding that the informed-consent document was inadequate, but alleged that OHRP had "failed to demand adequate and meaningful corrective actions by HHS, the medical centers that conducted this research, and the IRBs that reviewed and approved it."

After the group released its letter, SUPPORT and OHRP's determination received significant attention in the popular media and in professional journals. Prominent scholars, physicians, and bioethicists wrote to the editor of *The New England Journal of Medicine* expressing a range of views. Some argued that randomizing infants to different oxygen-saturation ranges within a standard of care may increase risk for study subjects.¹⁴ These individuals agreed with OHRP that the informed-consent documents used in SUPPORT were inadequate. Others argued that treatments within a standard of care, by definition, cannot increase risk; that the risk of death in SUPPORT was not supported by current research; and that all premature infants have an increased risk of death as a result of their condition.^{15, 16} These individuals considered OHRP's determination regarding the informed-consent document to be inappropriate.¹⁷

¹⁴ R. Macklin et al., "The OHRP and SUPPORT—Another View." *The New England Journal of Medicine*, 2013; 369: e3, June 26, 2013.

¹⁵ J.M. Drazen et al., "Informed Consent and SUPPORT." *The New England Journal of Medicine*, 2013; 368: 1929–1930, May 16, 2013.

NIH encouraged OHRP to withdraw its determination letter on SUPPORT, arguing that at the start of SUPPORT, researchers did not have scientific evidence to expect a difference in mortality between the two target ranges for oxygen saturation. Furthermore, NIH acknowledged that OHRP's determination letter has raised a larger issue: the question of how risks should be conveyed when the purpose of the research is to compare interventions that are all considered to be within the standard of care. According to NIH officials, the outcome of this debate "could affect how we conduct and communicate about critical research on interventions that are within the standard of care for all diseases and conditions."¹⁸

In response to the concerns of the research community and NIH, OHRP issued a followup letter to UAB on June 4, 2013. OHRP reaffirmed its decision that the informed-consent document was inadequate, but acknowledged the difficulty in defining reasonably foreseeable risks in research involving interventions considered to be within the standard of care. OHRP put on hold compliance actions against UAB relating to SUPPORT and committed to providing guidance on this topic.

On June 26, 2013, HHS announced a public meeting to be held August 28, 2013, on how regulations on human subjects protections should be applied to research on interventions within the standard of care. Issues for consideration included defining reasonably foreseeable risks and what should be disclosed to subjects in such research.¹⁹ The announcement also stated that HHS was considering changes to OHRP's compliance oversight procedures, including the use of experts during compliance reviews and the establishment of an administrative process for appealing OHRP's determinations.²⁰ HHS held this public meeting to gather input as it considered developing guidance on the topic. Twenty-seven individuals, including SUPPORT subjects' parents, bioethicists, physicians, and researchers, presented a range of views and provided feedback to OHRP on ways to improve oversight of human subjects protections.

FURTHER DISCUSSION

We offer the following observations based on this review and the events that have occurred since OHRP issued its determination letter in March 2013. Our observations relate to the retrospective nature of OHRP's compliance review of SUPPORT, OHRP's flexibility in its procedures for conducting reviews, and research comparing treatments within the standard of care.

¹⁶ D. Magnus and A.L. Caplan, "Risk, Consent, and SUPPORT." *The New England Journal of Medicine*, 2013; 368: 1864–1865, May 16, 2013.

¹⁷ B.S. Wilfond et al., "The OHRP and Support." *The New England Journal of Medicine*, 2013; 368: e36, June 20, 2013.

¹⁸ K.L. Hudson et al., "In Support of SUPPORT—A View from the NIH." *The New England Journal of Medicine*, 2013; 368: 2349–2351, June 20, 2013.

¹⁹ 78 Fed. Reg. 38343, 38345 (June 26, 2013).

²⁰ *Ibid.*

Retrospective nature of the SUPPORT review

OHRP's ability to influence directly the informed-consent process for a particular study is limited. Federal regulations rely on IRBs and research institutions, as well as the funders of research, to protect human subjects through initial determination of the ethics and merits of any particular study and through the informed-consent process.

OHRP received the complaint about the SUPPORT trial 2 years after patient enrollment in the trial had concluded. The study had been completed and the results had already been published. As a result, any actions that OHRP took could not have affected the course of the research, the informed-consent documents, or the enrollment of individual subjects in the study. Although OHRP's review of SUPPORT was retrospective, its determination letter addressed the institution's failure to include or adequately address reasonably foreseeable risks. The letter required the institution to provide a plan that its IRB will use to ensure and adequately address the basic elements of consent in future research involving human subjects, as required by Federal regulations. OHRP shared this determination letter with the other 22 institutions involved in the research and posted it on its Web site to educate those institutions about expectations for this type of research.

Flexibility in conducting compliance reviews

OHRP's 11-step process for conducting evaluations and the considerable discretion provided therein allow it to prioritize and shape its reviews in response to the specific circumstances of each allegation. OHRP can largely choose the specific allegations that it evaluates, as well as the content of any determination letters that it issues. Its compliance activities are not codified in Federal statute or regulations; rather, they appear in procedures issued by the agency.

In its review of SUPPORT, OHRP exercised its discretion to focus the evaluation on risks known at the start of the trial and on whether those risks had been communicated in the initial informed-consent document. Furthermore, in focusing its evaluation on the initial informed-consent documents, OHRP exercised its discretion not to review other aspects, such as whether any new risks were identified during the trial that should have been communicated to human subjects. Such risks might be found, for example, by the DSMC, which reviews data that might not be available to the funders of the research or to OHRP.²¹

Differing views on research comparing treatments within the standard of care

Finally, the discussions about SUPPORT have drawn attention to the protection of human subjects in research that compares treatments within the current standard of medical care. The goal of such research is to improve current knowledge and practice by determining the more effective intervention for diseases and conditions. OHRP's evaluation and

²¹ In our review, we became aware that OHRP may not have access to the minutes and records from the closed DSMC meetings. We are following up with OHRP to seek clarification on its authority to obtain all DSMC records when needed.

determination made public fundamental differences on this topic, not just within the research and patient advocacy community, but also among government agencies that fund and oversee this research.

For example, in an article published in *The New England Journal of Medicine*, NIH leadership wrote: “[W]e respectfully disagree with the conclusions of the OHRP, which we believe resulted from a fundamental difference in interpretations of how the regulations should apply to the state of scientific understanding when the SUPPPORT study commenced.”²² Given the differing perspectives of NIH and OHRP, HHS is reexamining this issue to better ensure that appropriate protections of human subjects are in place, while not discouraging progress in scientific research.

CONCLUSION

Our review of OHRP’s for-cause compliance evaluation of SUPPORT found that it followed its published procedures in conducting that evaluation. Those procedures are broad, meaning that the office has substantial discretion in how it carries out any one evaluation.

This report is being issued directly in final form because it contains no recommendations. If you have comments or questions about this report, please provide them within 60 days. Please refer to report number OEI-01-14-00560 in all correspondence.

Attachment

²² K.L. Hudson et al., “In Support of SUPPORT—A View from the NIH.” *The New England Journal of Medicine*, 2013; 368:2349-2351, June 20, 2013.

Attachment:

Chronology of OHRP's Evaluation of SUPPORT

(from OHRP's 5/24/11 receipt of complaint to UAB's 3/22/13 response to OHRP's determination letter)

2011

- May 24** OHRP receives an email complaint alleging that SUPPORT was unethical and researchers did not obtain informed consent from participants.
- May 25** OHRP confirms SUPPORT is funded by Eunice Kennedy Shriver National Institute of Child Health (NICHD) Neonatal Research Network and that OHRP has jurisdiction to conduct an evaluation.
- May 31** OHRP responds to the complainant acknowledging that the complaint was received and is under review.
- June 6** OHRP receives the SUPPORT protocol and informed-consent template from NICHD and conducts a preliminary review. OHRP identifies some preliminary concerns with the informed-consent document.
- July 7** OHRP initiates a conference call with NICHD to discuss the complaint.
- July 18** OHRP opens an evaluation by sending an inquiry letter to UAB (the lead institution of SUPPORT) and RTI (the SUPPORT data-coordinating center).
OHRP informs the complainant of its action the same day.
- Aug. 26** UAB responds to OHRP's inquiry letter, stating that it found no violations during its investigation.

2012

- Jan.** OHRP requests additional information from UAB, such as DSMC documents and clarification on aspects of SUPPORT.
- June** OHRP drafts its determination letter to UAB. OHRP asks for additional information from UAB and redrafts a few versions before finalizing.

2013

- Feb. 11** OHRP sends its final determination letter to UAB and RTI.
- Mar. 7** In response to RTI's request, OHRP removes RTI from the determination letter and reissues it.
- Mar. 22** UAB responds to OHRP's determination letter with corrective actions.