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Implications of the Revised Common Rule for Human Participant Research

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This paper looks at the implications of changes to the regulatory governance of human participant research that can be expected with implementation of the Revised Common Rule (RCR). The RCR refers to revisions of the existing federal regulations that govern the performance of research involving human subjects (ie, clinical research) in the United States and, under certain circumstances, when such research is also performed outside the United States. The term "common" is included because it refers to the fact that these regulations, often referred to as Code of Federal Regulations 46, is the common denominator regulations agreed to across a wide swath of federal agencies. CHEST 2019; 155(2):272-278

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The Revised Common Rule (RCR) has been in the making for almost a decade. It has taken this long to promulgate new human research participant regulations (the RCR continues the old language of human subject research), at least in part, because consensus building across the 15 Common Rule agencies, plus harmonization with the regulations of the US Food and Drug Administration and other relevant agencies, plus incorporation of matters raised in public commentary, remains an arduous task.

Although there have been delays in implementation of the RCR, it likely will ultimately go into effect in early 2019. Several changes that come with the RCR will alter the way human participant research is reviewed and conducted over the next 5 to 10 years. Regardless of one's involvement with human participant research, one must be able to read research reports and evaluate their design for scientific merit and ethical appropriateness; therefore, understanding the regulations that govern the ethical involvement of research participants is paramount.

The Common Rule, although revised slightly in 2009, has not had a substantive overhaul since the original human participant protections regulations were promulgated in 1991. The changes in the RCR run the continuum from no change at all, such as in the definition of minimal risk, to vast as in the changes to the infrastructure of the institutional review board (IRB) system.

ABBREVIATIONS: IRB = institutional review board; OHRP = Office for Human Research Protections; RCR = Revised Common Rule; sIRB = single institutional review board

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We look first at the implications of some of the changes to structure of the IRB system and, second, turn to some changes that are more specific for research participants. The third change is, arguably, the most significant addition to research that comes under the governance of these regulations and is related to the storage, management, and secondary research uses of private information and identifiable biospecimens (Table 1).

The purpose of these revisions is to improve the procedures that drive ethically and scientifically sound human participant research. The Executive Summary[1] makes clear that because the regulators believe, that "Since the Common Rule was promulgated, the volume and landscape of research involving human subjects has changed considerably," and that "research with human subjects has grown in scale and become more diverse" (p. 7150), these sweeping updates are needed. Some, such as the structural changes to the review process for multisite studies, represent a long overdue streamlining of the present, ponderous system.[2-5] Although the changes requiring the new single IRB (sIRB) system for multicenter trials are not due to go into effect until 2020, this transition is already starting. We predict that these structural changes will have major effects and result in significant improvements in the review process.

The success of the changes designed to improve consent practices for human participants depends on the quality of IRB membership, sense of regulatory responsibility of members and chairpersons, and depth of discussion. These factors are not new. Perhaps the RCR adds a bit more guidance and specificity to IRB considerations of consent processes. Only time and further evaluation of the newly configured IRB system will tell if the RCR has succeeded.

We conclude with suggestions for applying metrics that may quantify the progress the RCR has generated in improving quality regulatory review and oversight. Designing and applying methods for evaluation of the newly redesigned regulatory processes will be just as important as the formulation of the RCR.

Initial Introductory Literature

Several sources have enumerated the RCR changes in clear and orderly fashion.[1,6-8] For example, Chadwick[7] reviews the regulatory changes in the RCR on a section-by-section basis, underscoring that the definition of minimal risk has not changed. Hodge and Gostin[8] provide a particularly useful table with columns, going through the human participant research regulations on a pre- and postimplementation basis. These columns summarize the substance of RCR changes to informed consent, consent for secondary use studies of biospecimens, infrastructure changes to IRB review and the new, explicit exemptions for public health surveillance research. Menikoff et al[6] provide a more global approach. They make clear that the RCR did not

TABLE 1] Revised Common Rule: Key Challenges and Opportunities

Change	Challenge	Opportunity
Single IRB	Ensuring adequate training and that board membership has the depth, breadth, and diversity of knowledge to perform effectively	Streamlining the review process, eliminating redundancy
Informed consent and capacity	Making the informed consent process and documentation clearer and of greater benefit to research participants Ensuring special populations, including those with diminished decision-making capacity or educationally/economically disadvantaged potential participants, are well served by the RCR	Development of "capacity assessment teams" to help ensure protocols and informed consent process/documentation are optimized for the population being studied Recognition of the effect of non-medical determinants of health (socioeconomic factors) on the potential participant's ability/willingness to engage in clinical research. Designing studies to mitigate the negative effect of these factors
Biospecimens	Implementing the concept of "broad consent" for the future use of biospecimens	Create a nimble, secure, biorepository model equipped to address emerging research needs rapidly while respecting/protecting research participant autonomy and privacy
Evaluation of the RCR	Determining the benefits and limitations of the RCR; identifying points for future refinement	Use the delay in implementation to create a platform for anonymous prospective feedback from administrators, investigators, and research participants to assess the expected and unintended consequences of the RCR

IRB = institutional review board; RCR = Revised Common Rule.

adopt the controversial proposed change that would have required informed consent for use of unidentified biospecimens, which many researchers have found a relief.[9] As with Menikoff et al's article, the HHS.gov article is mostly focused on the expected improved efficiencies anticipated by the RCR.[1] A particularly helpful summary of the RCR changes has been produced by the American Society of Clinical Oncology.[10] Although produced for American Society of Clinical Oncology members, the summary is not oncology-specific, but offers a concise summary of the most important changes.

Given the complexity of the old regulations, their roots in the human participant research world, and the complexity of the RCR, such clarifications and summaries of the changes are much needed and we recommend this literature to you. In this paper, we take this literature as a jumping-off point. We do not summarize, but rather explore the RCR's potential for improving the quality and efficiency of the research review process for the decade ahead.

Single Institutional Review Board

From a structural perspective, the shift to a sIRB model is long overdue. This IRB evolution for US multicenter trials, although having an elongated lead-up to implementation, will make the IRB process significantly simpler and smoother for participants. Essentially, the sIRB process will function as an "IRB-of-record" system for US studies with multiple sites. A great burden will be lifted off the shoulders of many IRBs, especially those at acute care hospitals where many multisite studies are conducted in the United States. In the new system, basically the location of the principal investigator, assuming the federal government does not object to the selection, will be the site of the sIRB. When minor changes need to be made to a protocol, which invariably occur when a protocol begins enrolling participants, the changes will be evaluated by the sIRB as the IRB-of-record. Implementation of the changes by the IRBs at the participating institutions will simply be an administrative function. The sIRB will provide for the long-awaited streamlining of review and implementation of protocol amendments.

IRB administrators and the institutional officials responsible for human participant research may find the preparations to shift to this new sIRB system for US multicenter trials onerous at the outset. The many institutions that now contribute to the performance of multisite human participant research will be affected by the change from a local to an sIRB. At the local level, there may be concerns about what might be lost by moving to a more centralized and/or regionalized IRB system.[11] It is hoped that the perceived benefits will outweigh the potential concerns regarding the selection and use of an sIRB.

The increased process efficiencies are not limited to sIRB reviews of multicenter studies. RCR changes to the annual and ongoing review processes of all studies under Common Rule governance, whether at a sIRB or local IRB, set the expectation that not taking the IRB members' time to do reviews of little effect can result in time better spent. The RCR all but eliminates continuing reviews, where continuing and/or annual reviews are functionally noncontributory to improving human participant protections. What the RCR has termed "limited IRB review" in the section on Exempt Research will help streamline the regulatory process, as will the RCR's relaxing changes to the continuing review process. Additionally, there is now a regulatory commitment to review and update the expedited category list every 8 years so the RCR has built into it ongoing attention to improving efficiencies through keeping up with progress.

Informed Consent and Capacity

Focusing on the changes that are more research participant-specific than the structural changes just discussed, the most notable address the informed consent process. For example, the changes to the definition of "vulnerable" that removes "pregnant women" and substitutes "impaired decision-making capacity, or economically or educationally disadvantaged" for "handicapped or mentally disabled persons" are not merely changes for the purpose of updating to more politically correct language. Rather, these changes should force IRB members to examine more thoroughly the particular study population, or study catchment area possibilities, so as to require investigators to build specific protections for vulnerable populations into the protocol.

When a protocol includes those who are in the vulnerable or potentially vulnerable categories (eg, economic or educational factors) additional protections are needed. One of the most important yet underused ways the present regulations suggest increasing IRB review competence is to invite people with specialized expertise and/or advocacy backgrounds related to the

study population to join the IRB discussions. This approach might have governed some IRBs in the past, but the need for consideration is addressed up front.

Another approach to increasing IRB review competence for these specialized populations would be to review other research ethics guidance documents where they specifically address the issues not specified in the US regulations. That is, per research ethics convention,[12,13] when one nation's regulations of clinical research are not as specific or stringent as others, the more specific and/or stringent regulations might ordinarily serve as a guide for research review.

Research involving adults with decisional impairments presents an ideal case study. Although the RCR calls for study populations, or individual study participants, who lack decision-making capacity to be permitted in human participant research, there are no protections that are specifically delineated other than obtaining consent from a legally authorized individual.[14] Additionally, because the Declaration of Helsinki[15] does offer such specifications, it could be useful in consideration of ethical issues pertaining to involvement of study participants and/or populations in a protocol not bound by the Declaration. In the section on Vulnerable Groups and Individuals, Helsinki requires that, "All vulnerable groups and individuals should receive specifically considered protections."[15] Subsection 20 of this section states, "Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research."[15] The Declaration of Helsinki also goes on to discuss requirements for assent in this population.

Just because the RCRs do not specify particular protections for this vulnerable population, involvement of participants lacking decision-making capacity, or in the case of studies involving individuals who are or may be economically and/or educationally disadvantaged, discussions can address what special protections ought to be incorporated into the protocol. When participants who lack decision-making capacity are to be included, IRB members will need to make certain that the study design includes sound methodology for assessment of decision-making capacity.[16-18]

For studies involving economically disadvantaged participants, the RCR enhancements to the informed consent process will call on IRBs to consider how this particular vulnerability affects the informed consent process. How might a protocol be reshaped to minimize burdens and the impact that disease, particularly serious chronic disease, has on patient's decision-making when it comes to clinical trial participation? Factors may include time needed off from work, transportation/parking, child/elder care, and presence/absence of high-quality standard-of-care treatment options available closer to home.

For educationally disadvantaged participants, how ought communications with them be structured? How much time will be required to help them work through a long and complicated consent process? What kinds of educational aides, if any, might be built into the protocol to provide extra supports? How is understanding going to be assessed?

For all these populations, who is going to be working through the informed consent process with the potential participants? Is the principal investigator involved in the patient's clinical care? If so, how does the protocol create safeguards to avoid conflicts of commitment? Does the protocol have a medically responsible physician/other clinician who is outside the study but responsible for the clinical care of the participants?

The need for these kinds of IRB discussions has existed since research review began; however, not all IRBs have had such conversations when the protocols under review call for such depth. The RCR changes are designed to produce such conversations and to strengthen protections for participants. Unlike the administrative changes of the RCR, such as moving multicenter trials from the exhaustive and unnecessary repetitiveness of redundant reviews to a sIRB model, reducing inconsequential annual and continuing review burdens, and expanding the exemptions list, implementing the informed consent changes delineated in the RCR in a meaningful manner are a significant challenge of paramount importance.

Requiring an opening paragraph or two that summarizes the key considerations of a study does not necessarily mean that such a summary will really speak to whats is important for any particular potential participant or result in a more effective consent process. Likewise, requiring that portions of the consent form be organized and presented in a uniform way to facilitate comprehension is laudable but is unlikely to reduce the length or improve utility of the document. The quality of the ethics of design and implementation still rests, as it always has, on the competence and conscientiousness of

the IRB members and the depth of IRB discussion. This is true regardless of whether the study is a traditional clinical trial or a newer type of study, as are many of the biospecimen studies.

Biospecimens

The introduction of biospecimens into the human research participant regulatory system may turn out to be the most far-reaching addition of the RCR. The rapidly expanding realm of "precision medicine" and its basic/translational science correlates has made specimen and data warehousing a critical component of research programs across the country. One of the important changes that accompanied the inclusion of biospecimens into the regulatory process is in the section on definitions. This potentially far-reaching novelty of the RCR is the requirement for regular (1 year after study initiation and every 4 years thereafter) reevaluation of whether investigators have kept up with the most appropriate "analytic technologies or techniques" to use in generating "identifiable private information." This essentially means that there will be a regular technology reassessment for protocols involving biospecimens.

Because it is often difficult to imagine the span of secondary studies one might want to conduct before a primary protocol is collecting data, the RCR regulators have created a mechanism of "broad consent" as an alternative to standard informed consent for some biospecimen studies. Following the introduction of this terminology in the section on General Requirements for Informed Consent, there is guidance on what this "broad consent" requires when the protocol is initially reviewed. But there may be problems if IRBs do not take seriously their own needs for self-education. Quality of informed consent for more traditional clinical trials has been long known to be variable, which is why the RCR has circled back on its original regulatory requirements and attempted to strengthen the language for designing informed consent processes.

When thinking about this vast new expanse of human participant research, one that IRBs have had little or no experience reviewing, the term "broad consent" gives one pause in thinking about how it all might play out. One can imagine some investigators simply asking for use of these samples and data for future use, with just a few sentences added about how the samples and data will be stored, maintained, and accessed. But one hopes for more than that.[19,20] It is likely, given the increasing affordability of sequencing technology, that what today may be accurately described as anonymized samples, will in future be samples that are identifiable.

One also can see the demand on the horizon for physicians in all therapeutic areas to get samples genetically analyzed for the specific purpose of obtaining genetic information that might be of use to the patient. Anonymizing the samples will not be of high utility in these cases; rather, these studies are central to the progress of the movement of translational research. To meet these translational research goals, it will be important to maintain personally identifying information because that is the information most helpful to patients and their treating physicians, but the RCR has intentionally steered clear of these kinds of samples.

One example for addressing this issue comes from the area of genetic eye diseases. The National Ophthalmic Disease Genotyping and Phenotyping Network, is a partnership between the National Eye Institute of the National Institutes of Health and a network of eye clinics and laboratories across the vision research community and called eyeGENE. Established in 2005, eyeGENE has been a revolutionary translational research program.

Under eyeGENE in particular, if a patient has an eye condition that his or her ophthalmologist suspects is the result of a genetic disease, and if the patient and the patient's community physician are willing to enroll in eyeGENE as research participants, both become, technically, study subjects. The technicality is that because the patient is giving his or her tissue and data to eyeGENE, ultimately for research purposes, the patient and physician must be considered research participants, but the driver for participation in eyeGENE may legitimately be explained as clinical care.

With the requirement for all eyeGENE network researchers to have Clinical Laboratory Improvement Amendments (CLIA)–approved laboratories, the researchers are allowed to return clinical information in a report to the treating community-based physician-investigator. This allows the treating ophthalmologist to resume his or her original position as a clinical care provider and give a clinical report back to the patient.

As for the eyeGENE network investigators, after producing the report for the community ophthalmologist, they have exclusive use of the remainder of the sample for their own research for 6 months. After that, any remaining tissue, along with its attendant phenotypic and other personally

identifying data, go into an open-source repository to which any bona fide investigator can submit a research protocol of any design they wish, including a study using all the personally identifying information.

eyeGENE is revolutionary because clinical need drives the creation of research material, reducing the creation of one-off studies in which the samples are used for a particular protocol only and then often left in a university freezer unusable for any other studies. This design, unlike the one-off model, is a Mobius strip that meets the ideal of translational medicine in a bidirectional feedback loop; that is, the bidirectionality is of meeting clinical need while creating a vast array of personally identifiable samples in an open-source research database.

The RCR's weaving of biospecimen research so thoroughly throughout the new regulations suggests that the harnessing of clinical need to power research material accrual may spur translational human participant research. Certainly, there remain justice concerns, because not all research participants will be asked to donate to biobanking and not all those who do will be able to access the off-label or novel therapies derived from their research participation. These injustices of society, mirrored in the clinical research world, demand the attention of research ethicists, investigators, administrators, and concerned others. Nonetheless, perhaps bringing biospecimens and secondary analyses of accompanying personally identifiable data under the umbrella of 45 Code of Federal Regulations 46 can produce a tipping point. Through processes of enhanced IRB discussion, and with thoughtful application of the RCR's notion of "broad review,"[21] these changes to the human participant research regulations landscape may result in the creation and maintenance of well-designed and conducted research programs such as eyeGENE for every therapeutic area to benefit present future patients simultaneously.

Exclusions From RCR Review

As rare as research programs such as eyeGENE are, quality improvement studies are ubiquitous. Just as the RCR and its subsequent guidance documents make more clear what is not research, there are IRB review implications for what is research. The RCR explanatory literature previously cited make note of the excluded activities delineated in the RCR. There has been enough confusion about this section of the RCR, however, that the Office for Human Research Protections has issued a draft clarifying guidance about what kinds of work is excluded from IRB oversight.[22,23] Of relevance here is what might turn out to be unintended consequences of these exclusions. It is possible that the emphasis placed in the RCR on what is not research may make investigators in the health services research world more punctilious about bringing what is ordinarily referred to as quality assessment/quality improvement research to the IRB. That includes the newer version advanced by the US Agency for Healthcare Research and Quality, referred to as research designed for the learning health care system. So much of such research is not sent to IRBs, if only for a formal letter of exemption; perhaps the new attention to what is not covered may encourage greater attention to what should undergo IRB review.[24]

Conclusions

Even though RCR implementation has not yet begun, it is coming. This extra time before implementation can be well used thinking forward to where one wants to be and how to get there. One of the most important views forward is to plan for the evaluation of the effectiveness of the RCR. We suggest that the Office for Human Research Protections (OHRP) use this time to develop an in-depth evaluation program of the new regulations. We recognize that there are constraints on federal government agencies sending out paper questionnaires and limits to the effectiveness of these surveys. A workaround could be that OHRP apply its own RCR to its thinking about how to evaluate regulatory efficacy and use new technologies, such as Web-based technologies, to anonymously collect and evaluate data about RCR effectiveness in increasing quality and efficiency in human participant research.

We believe such evaluation research fits comfortably within the RCR section on Exempt Research[1] that allows for "…Research…projects that are conducted…by a Federal department or agency…that are designed to study, evaluate, improve…public …service programs." Surely, human participant research regulations can be characterized as a public service program. Conducting clinical research designed to produce knowledge and improve the health care of future patients certainly serves the public's health needs.

To evaluate the RCR's effectiveness in the two main areas of improved quality of review and improved efficiency in meeting that end, data need to be collected about how IRB members, chairpersons, administrators, research participants, and investigators think about the implementation of the RCR.

Questions to answer about the RCR include the following.

1. What do IRB members (eg, chairpersons, administrators, research participants, investigators) think have been the greatest strengths of the RCR?
2. What have been its weaknesses?
3. What unintended consequences has the RCR produced?
4. What have been the reactions of
   A. people in your institution and
   B. systems in which you work to the RCR implementation?

It will be important that data collected from IRBs be organized so that it can be subjected to a meta-analysis. The sweeping changes to the RCR, and the importance of its mission, call for a well-organized evaluation process.

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References

1. HHS.gov. Revised Common Rule. 2017. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html. Accessed March 28, 2018.
2. Check DK, Weinfurt KP, Dombeck CB, Kramer JM, Flynn KE. Use of central institutional review boards for multicenter clinical trials in the United States: a review of the literature. *Clin Trials*. 2013;10(4):560-567.
3. Klitzman RL. Local IRBs vs. federal agencies: shifting dynamics, systems, and relationships. *J Empir Res Hum Res Ethics*. 2012;7(3):50-62.
4. Blustein J, Regenstein M, Siegel B, Billings J. Notes from the field: jumpstarting the IRB approval process in multicenter studies. *Health Serv Res*. 2007;42(4):1773-1782.
5. Maloney DM. Alternatives to local institutional review board (IRB) system debated. *Hum Res Rep*. 2006;21(4):1-2.
6. Menikoff J, Kaneshiro J, Pritchard I. The Common Rule, updated. *N Engl J Med*. 2017;376(7):613-615.
7. Chadwick GL. New final Common Rule published: many changes are required. 2017. http://files.constantcontact.com/7ad07d0b001/7bd1f2ce-05e8-4d6a-bd2a-eaac1a6e9e25.pdf?ver=1485629966000. Accessed March 28, 2018.
8. Hodge JG Jr, Gostin LO. Revamping the US federal Common Rule: modernizing human participant research regulations. *JAMA*. 2017;317(15):1521-1522.
9. Lynch HF, Meyer MN. Regulating research with biospecimens under the revised Common Rule. *Hastings Cent Rep*. 2017;47(3):3-4.
10. American Society of Clinical Oncology. Federal policy for the protection of human subjects "Common Rule": summary of final Rule. 2018. https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/pdf/2018-asco-common-rule-summary.pdf. Accessed June 16, 2018.
11. Klitzman R. How local IRBs view central IRBs in the US. *BMC Med Ethics*. 2011;12:13.
12. Emanuel E, Wendler D, Grady C. *The Oxford Textbook of Clinical Research Ethics*. New York: Oxford University Press; 2008.
13. London A. *Clinical Equipoise: Foundational Requirement of Fundamental Error?*. New York: Oxford University Press; 2007.
14. Karlawish J. *Research on Cognitively Impaired Adults*. New York: Oxford University Press; 2007.
15. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
16. Appelbaum PS. Clinical practice. Assessment of patients' competence to consent to treatment. *N Engl J Med*. 2007;357(18):1834-1840.
17. De Vries R, Ryan KA, Stanczyk A, et al. Public's approach to surrogate consent for dementia research: cautious pragmatism. *Am J Geriatr Psychiatry*. 2013;21(4):364-372.
18. Bailey DB Jr, Raspa M, Wheeler A, et al. Parent ratings of ability to consent for clinical trials in fragile X syndrome. *J Empir Res Hum Res Ethics*. 2014;9(3):18-28.
19. Appelbaum PS, Fyer A, Klitzman RL, et al. Researchers' views on informed consent for return of secondary results in genomic research. *Genet Med*. 2015;17(8):644-650.
20. Appelbaum PS, Parens E, Waldman CR, et al. Models of consent to return of incidental findings in genomic research. *Hastings Cent Rep*. 2014;44(4):22-32.
21. Kaufmann P, O'Rourke PP. Central institutional review board review for an academic trial network. *Acad Med*. 2015;90(3):321-323.
22. NIH. OHRP Announces Availability of three draft guidance documents related to revised Common Rule. 2018; https://osp.od.nih.gov/2018/07/27/ohrp-announces-availability-three-draft-guidance-documents-related-revised-common-rule/. Accessed September 3, 2018.
23. HHS.gov. Scholarly and journalistic activities deemed not to be research: 2018 Requirements. 2018. https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-scholarly-and-journalistic-activities-deemed-not-to-be-research/index.html. Accessed September 3, 2018, 2018.
24. Nerenz DR, Stoltz PK, Jordan J. Quality improvement and the need for IRB review. *Qual Manag Health Care*. 2003;12(3):159-170.