Research Consent at the Age of Majority: Preferable but not Obligatory

Kyle B. Brothers, MD, PhD,[a] Benjamin S. Wilfond, MD[b,c]

abstract

In this issue of *Pediatrics*, Berkman et al argue that parental permission to obtain samples is sufficient to continue storing them and using them for research after the pediatric participant reaches the age of majority. In this Ethics Rounds, we argue that there are important ethical reasons for obtaining consent from participants when they reach majority. However, these reasons must be balanced with the aim of efficiently and economically conducting research that benefits children. Given current guidance from the relevant regulatory bodies, it remains necessary to obtain consent for the continued use of identified pediatric samples when participants reach the age of majority unless the institutional review board grants a waiver of consent. However, we argue that waivers of consent should more frequently be granted by institutional review boards and used for this purpose.

Are investigators obligated to obtain consent from pediatric biobank donors when they reach the age of legal majority? In this issue of *Pediatrics*, Drs Berkman, Howard, and Wendler[1] make a persuasive case that the authority of parents can permit the use of pediatric biobank samples after the donor has reached adulthood. Although we substantially agree with this conclusion, we believe the authors overstate some of the concerns others have raised about the continued use of pediatric samples and understate the ethical and regulatory implications of their proposal. Furthermore, there are small ways that institutional review boards (IRBs) can change their practice to support pediatric biorepository research that is efficient and scientifically valuable while continuing to meet current regulatory requirements and ethical goals.

In this Ethics Rounds, we consider the same case described by Berkman et al.[1] Considering ethical and regulatory issues in turn, we conclude that parental permission does carry adequate authority to continue using pediatric samples once the donor reaches the age of majority. On the other hand, there are still important ethical reasons to obtain consent at this age. When these considerations would significantly limit the practicability of research, however, current regulations provide 2 potential paths for continuing to use pediatric samples after the donor has reached the age of majority.

BENJAMIN S. WILFOND COMMENTS

Parental permission for research participation is rooted in the important authority that parents have to make decisions for young children, who do not have the capacity to provide informed consent. For most of childhood, pediatric research participants do not have the ability to understand information about the risks and benefits of research participation, nor do they have the capacity to make voluntary decisions about assuming these risks. Typically developing children develop these abilities over time, although the timing for this development is variable.

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Human development is a continuous process that takes place in fits and starts across the entire course of human life, and it occurs at different rates for different individuals. Developmentally speaking, an adolescent's 18th birthday is just another day.

Based on this understanding of child development, it is somewhat intuitive to assume that children should gradually be offered opportunities to make important decisions as they develop the capacity to do so. This is, in fact, a fundamental principle of pediatric research ethics. It is why we offer adolescents the opportunity to assent to their research participation at the time of enrollment, and it is the principle that underlies the majority view that pediatric research participants should be offered the opportunity to provide consent when they reach adulthood.

As Berkman et al[1] point out, however, that current practice does not fully reflect this important principle of pediatric research ethics. If we were to emphasize the autonomy of children above all other considerations, we would require investigators to provide information about the study over time as pediatric participants incrementally develop the ability to understand the implications of research participation. As it became appropriate, adolescents participating in research would be asked to add their assent and later be offered the opportunity to provide informed consent.

Current practice is clearly imperfect. At least some of these imperfections, however, reflect the need to balance priorities. Although respecting the developing autonomy of children and adolescents is an important principle of research with children, it is not the only factor that needs to be considered. One of the economic and scientific advantages of biorepositories is that they make biosamples and health data available for a large number of research studies while limiting the need for continued contact with the individuals who donated these resources. Because pediatric research provides an important public good, it is reasonable to weigh the cost-efficiency and practicability of research against the important principle that investigators should respect the developing autonomy of pediatric research participants.

Although there are no systematic studies on IRB practices related to the use of biospecimens when children become adults, we have previously published findings that indicate there is significant variation across institutions.[2] Some IRBs readily will waive the requirement for consent so that biorepositories can continue to use identifiable samples; others require investigators to destroy samples if donors cannot be reached for their consent.

There can be little doubt that the current array of practices is less than ideal, and some practices are simply unjustified. For example, many IRBs require investigators to destroy data and samples if pediatric biorepository participants cannot be reached when they reach the age of majority, although there are a number of alternatives that would preserve the value of these samples to research.[2] This practice highlights how important it is to understand and respect the role of parental authority; Berkman et al[1] have provided important insights on this issue. There are many parental decisions that are not revisited as children reach adulthood, and this enduring influence of parental decisions is an unavoidable result of parental authority during childhood. Although respect for children's developing autonomy is an important principle in pediatric research ethics, parental authority provides a suitable basis for continuing to use identifiable stored samples for research after children reach the age of majority.

However, the importance of parental authority does not negate the many important reasons for seeking consent from former pediatric biobank donors when possible. First, the informed consent process provides an opportunity to nurture the developing autonomy of adolescents and young adults. Second, it can help young adults understand the value they bring to biomedical research and may encourage them to participate in future research. Third, and perhaps most importantly, seeking consent can demonstrate respect for the young adult. However, these are ethical justifications for choosing to seek consent, which is different from an ethical requirement to affirmatively obtain consent.

A survey of 1186 patients at 5 academic medical centers found that 54% of respondents supported Berkman et al's[1] view that researchers should not have to ask for consent.[3] Of those who thought that researchers should seek consent, 44% thought that it was acceptable to continue to use samples when the donors could not be reached. These data suggest that the extremes of not attempting consent (as proposed by Berkman et al[1]) or requiring consent may leave significant proportions of the public dissatisfied. The middle-ground approach would be to seek consent but not require consent to continue using samples. This approach will not satisfy all, but it may be a compromise approach that balances concerns on both sides.

Berkman et al's[1] analysis still supports the conclusion that it is not always necessary to obtain consent at the age of majority. Sometimes this is not practicable, and in those cases, parental authority provides a valid, ethical justification for continuing to use stored research samples and data when donors cannot be located. As we will explore in the next section,

the current regulatory scheme fits this ethical framework relatively well. However, it does not allow for the radical change in practice proposed by Berkman et al.[1]

KYLE B. BROTHERS COMMENTS

Over the past 6 years, a significant effort was undertaken at the US Department of Health and Human Services to revise the Common Rule, the federal regulations that IRBs must follow when overseeing human subjects research. This effort was framed primarily as an effort to modernize these regulations to accommodate new types of research, such as biorepositories, that were not anticipated when the regulations were first promulgated.[4,5] After a lengthy and animated debate about these controversial revisions, the Obama administration finalized the revised Common Rule in its final days. Although the Trump administration currently has the final rule on hold, the director of the Office for Human Research Protections (OHRP) has predicted that these regulations will eventually be enacted as proposed.[6]

This background highlights how unlikely it is that we will see further revisions to the Common Rule anytime soon. The proposals that were disseminated over the course of this recent modernization effort proved to be remarkably controversial and ultimately resulted in a final rule that was widely considered to represent only a minor update to the original regulations.[7] Given this recent history, there is little energy in the regulatory and health policy community to start this process anew. If it were necessary to revise the Common Rule to allow for the change in practice that Berkman et al[1] propose, it is unlikely that such a revision will be seriously considered in the next decade.

However, they argue that such a change is not necessary and that the current regulations would permit investigators to continue using identifiable stored biosamples and health data with neither informed consent from the pediatric donor nor a waiver of consent. They argue, in effect, that although the collection of identifiable biosamples and data constitutes human subjects research, the ongoing storage and use of these biosamples and data falls outside this regulated category. To support their claim, they reference the language of the Common Rule, in which a research subject is defined as a "living individual about whom an investigator conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information."[8] The majority interpretation of this language has been that as long as an investigator possesses identifiable private information about a donor, the donor remains a human research subject. Berkman et al[1] offer an alternative interpretation, concluding that pediatric biorepository donors are human research subjects at the time they are enrolled in a biorepository and their biosamples and data are collected, but afterward, the storage and use of these identified resources do not constitute human subjects research.

These authors are not the first to recognize the ambiguity in this language. In fact, 1 of the most controversial proposals that was debated during the effort to revise the Common Rule was intended to address whether the storage and use of biological samples should constitute human subjects research regardless of the presence of identifiers.[4] Because this proposal was (fortunately) not adopted, the ambiguity remains.

Given that the revision to the Common Rule did not provide such a clarification, and there is no reasonable chance that further revisions will be made in the near future, IRBs must decide how they will interpret this language. And this is, unfortunately, where the otherwise reasonable proposal put forth by Berkman et al[1] encounters significant barriers. Although individual institutions and IRBs are free to adopt practices that they believe are most consistent with the regulatory requirements of the Common Rule, from a practical perspective, they depend on the OHRP to provide guidance on how the Department of Health and Human Services interprets its regulations and thus how IRBs would be evaluated if they were to be audited.

Put simply, despite the ambiguity in the current language of the Common Rule itself, the OHRP has promulgated guidance in a variety of forms that instructs IRBs to treat research on identified samples as human subjects research and seek informed consent when pediatric biorepository donors reach the age of majority. In a frequently asked questions Web page addressing research with children, the OHRP explicitly addresses this issue under the question, "What happens if a child reaches the legal age of consent while enrolled in a study?":

[I]f the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of "human subjects research" (for example, it involves the continued analysis of specimens or data for which the subject's identity is readily identifiable to the investigator[s]), then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects.[9]

This interpretation is rooted in the OHRP's broader interpretation of the way the Common Rule should be interpreted in the context of biorepository research. Specifically, the OHRP distinguishes between noninterventional research using deidentified samples (which is not regulated as human subjects research) from research using identified samples (which is regulated as human subjects

research).[10,11] In other words, the OHRP has not just arbitrarily decided that informed consent is required when pediatric biorepository donors reach adulthood. This conclusion is integral to its overall interpretation of the Common Rule with respect to regulating research that uses identifiable stored samples. The revision of a single frequently asked question would not be enough to effect a change in this area. Given the overall consistency of the OHRP's interpretation of the Common Rule, it would be necessary to adopt an entirely new framework that would change its guidance on a range of issues related to biorepository research.

KYLE B. BROTHERS AND BENJAMIN S. WILFOND CONCLUDE

Berkman et al[1] argue that biorepository samples collected with parental permission should be available for continued research use when pediatric donors reach the age of majority, and it is not necessary to reach out to pediatric donors for their consent. Our disagreement is partial, in that we would highlight the value of contacting pediatric donors when this would not detract from important research aims. We agree on 2 important conclusions, however. First, we believe that it is scientifically important to ensure that identified biorepository samples can continue to be used once donors reach the age of majority. Second, we do not believe there is a compelling reason to require that investigators take on the substantial cost and effort to maintain contact with pediatric participants for the sole purpose of contacting them for their consent when they reach the age of majority. If these goals are unlikely to be achieved through a revision to the Common Rule or a reframing of the OHRP's interpretation of the regulatory language, are other options available?

We believe there are at least 2 alternatives that will similarly limit the burden on biorepositories. The first alternative is for biorepositories to deidentify stored samples and data. Under the OHRP's current interpretation of the Common Rule, biorepository donors are not considered human subjects once their samples and data are deidentified.[11] Informed consent is thus not required from pediatric biorepository donors to continue using their deidentified samples and data once they reach the age of majority. This still allows for a number of possibilities. If keeping samples and data identified for a time would be useful to the biorepository, deidentification can wait until each participant reaches the age of majority. Alternatively, biorepositories can use a 1-way hash to deidentify samples but retain the ability to add new data longitudinally.[12]

The second alternative is to obtain a waiver of consent from the IRB so that identifiable samples can be retained.[13] A waiver of consent is only possible when the research is not practicable if informed consent is required. Despite a letter from the Secretary's Advisory Committee on Human Research Protections intended to clarify this standard,[14] it seems that IRBs often face difficulty in identifying when a requirement for informed consent at the age of majority should be considered impracticable. This explains why some IRBs are reticent to waive consent for this purpose. However, this is a matter of variation in local interpretation, which can be easily addressed by the OHRP or even through scholarly discourse, such as this Ethics Rounds case. IRBs can, and should, apply a more reasonable interpretation of practicability when considering requests for waiving consent in the context of pediatric biorepositories.[13] This is workable now, and no revision to the Common Rule or the OHRP's guidance framework is required.

Berkman et al[1] raise a number of concerns about this waiver-of-consent approach. However, in the current regulatory environment, all of these barriers can be readily addressed by IRBs. They note, for example, that investigators cannot know ahead of time whether IRBs will be willing to grant a waiver of consent later. This is why we recommend that biorepositories develop a plan for how they will manage donors' transition to adulthood and receive prospective IRB approval for this plan at the time of implementing the biorepository.[13] Not only does this approach allow IRBs and investigators to agree on a reasonable approach from the beginning, it also allows investigators to share this information with pediatric donors and parents during the informed consent process. For example, they could plan to attempt contact for consent based on the address at the time of enrollment (or updated via the family) coupled with a plan to continue to use samples under a waiver of consent from those who cannot be contacted.

Admittedly, neither of these alternative solutions is ideal. The current regulatory framework is imperfect, and these alternative approaches reflect that imperfection. However, they do offer realistic opportunities to solve a vexing problem in pediatric biorepository research. By providing guidance on these options,[13] we hope that more pediatric biorepositories will be created and that knowledge to inform pediatric care can be generated in ways that are quicker, more efficient, and more economical.

All of the cases in Ethics Rounds are based on real events. Some incorporate elements of a number of different cases in order to better highlight a specific ethical dilemma.

ABBREVIATIONS

IRB: institutional review board
OHRP: Office for Human Research Protections

REFERENCES

1. Berkman BE, Howard D, Wendler D. Reconsidering the need for reconsent at 18. *Pediatrics*. 2018;142(2):e20171202
2. Brothers KB, Lynch JA, Aufox SA, et al. Practical guidance on informed consent for pediatric participants in a biorepository. *Mayo Clin Proc*. 2014;89(11):1471–1480
3. Goldenberg AJ, Hull SC, Botkin JR, Wilfond BS. Pediatric biobanks: approaching informed consent for continuing research after children grow up. *J Pediatr*. 2009;155(4):578–583
4. Department of Health and Human Services. Federal policy for the protection of human subjects. *Fed Regist*. 2015;80(173):53933–54061
5. Hudson KL, Collins FS. Bringing the common rule into the 21st century. *N Engl J Med*. 2015;373(24):2293–2296
6. Office for Human Research Protections. SACHRP Meeting; May 25–26, 2017. Available at: https://www.hhs.gov/ohrp/sachrp-committee/meetings/2017-may-25-26/index.html. Accessed July 20, 2017
7. Rivera SM, Brothers KB, Cadigan RJ, et al. Modernizing research regulations is not enough: it's time to think outside the regulatory box. *Am J Bioeth*. 2017;17(7):1–3
8. US Department of Health and Human Services. Definitions: human subject. *45 CFR §46.102(f)* (2009)
9. Office for Human Research Protections. Frequently asked questions: What happens if a child reaches the legal age of consent while enrolled in a study? 2011. Available at: http://answers.hhs.gov/ohrp/questions/7270. Accessed January 14, 2013
10. Office for Human Research Protections. *Guidance on Research Involving Coded Private Information or Biological Specimens*. Rockville, MD: Office for Human Research Protections; 2004
11. Office for Human Research Protections. *Guidance on Research Involving Coded Private Information or Biological Specimens*. Rockville, MD: Office for Human Research Protections; 2008
12. Roden DM, Pulley JM, Basford MA, et al. Development of a large-scale de-identified DNA biobank to enable personalized medicine. *Clin Pharmacol Ther*. 2008;84(3):362–369
13. Brothers KB, Holm IA, Childerhose JE, et al; Pediatrics Workgroup of the Clinical Sequencing Exploratory Research (CSER) Consortium. When participants in genomic research grow up: contact and consent at the age of majority. *J Pediatr*. 2016;168:226.e1–231.e1
14. Tilden S. *January 31, 2008 SACHRP Letter to HHS Secretary: Recommendations Related to Waiver of Informed Consent and Interpretation of "Minimal Risk."* Washington, DC: Office for Human Research Protections; 2008

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