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FEATURE ARTICLE

Recontacting Pediatric Research Participants for Consent When They Reach the Age of Majority

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Pediatric research raises particular ethical and legal issues due to the fact that children are presumed to have insufficient cognitive ability to consent to participate in research.[1] In some countries the legal age of majority is recognized as the age at which children can provide consent for research participation, though in others the age of consent for research is established by policy guidance which stipulates an age of consent or sets the criteria for determining cognitive capacity (maturity). For children who have not reached the age of consent as established by law or policy, parents (or legal guardians) must authorize their participation. Depending on their age and maturity, children whose parents or guardians authorize research participation may be asked to assent to being enrolled in a study.

The ethical and legal norms governing research generally maintain that consent is a continuing process.[2] Research involving children may include studies spread over a number of years (e.g., biobank or longitudinal studies). Thus, it is likely that children who mature during the course of a study acquire the cognitive capacity to decide whether or not they want to continue their participation. The purpose of this paper is to explore the issue of whether, to satisfy the ethical and legal norms of consent for research, participants in pediatric studies who attain the age of majority after their parents or guardians enroll them in a study should be "recontacted" to obtain their consent to remain in it. After summarizing the legal and policy landscape regarding the age of consent for research participation and clinical care, we explain why the issue of recontacting participants of pediatric research when they reach the age of majority is important and ask whether there is an ethical obli-

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gation to do so. We then illustrate the complexities of answering this question in three research contexts: longitudinal pediatric studies (which could include biobanking), pediatric clinical trials, and possible future research with newborn screening bloodspots conducted during the lifetime of individuals' whose bloodspots are used.

Legal Age of Majority for Consent in Research and Clinical Settings

Very few countries explicitly legislate an age of majority specific to consent in the research context.[3] In the province of Quebec in Canada, amendments to the Civil Code in 2014 stipulate that a local research ethics committee may allow minors aged 14 years or over to independently give consent to research, but only if the research is of minimal risk and the circumstances justify it.[4] In the Netherlands, minors aged 12 years and older can legally consent to research, but the parents must consent as well, thus creating a form of dual consent up to 16 or 18 years of age, depending on the type of research and on contextual issues in the clinical setting.[5]

In the context of clinical trials, the 2014 European Union (E.U.) Clinical Trials Regulation provides some guidance for minors by simply mandating that consent should be obtained upon achieving "legal competence": "If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial."[6] However, other than this clinical trial legislation, which is binding in all E.U. countries and a handful of countries that specifically legislate the age of majority for research, there is little guidance regarding the legal determination of "majority" in the research context, and so the legal age of majority for adulthood is generally relied on.

Some countries fill this legislative void by using the ethics and professional policies that govern research and allow for a professional case-by-case determination of maturity. In these countries, researchers need to determine whether the adolescent understands not only the potential risks but also the impact, long-term consequences, and lack of personal benefit of participation.[7] For example, the Canadian Paediatric Society states that "the capacity to provide meaningful consent matures beyond 14 years of age but is very limited before nine years of age. This points to a group of 9- to 14-year-olds who will be in transition—some fully able to provide consent and some unable, despite their physical advances in maturity."[8] Similarly, the Royal College of Paediatrics and Child Health in the United Kingdom states that the acquisition of capacity to consent to research is a developmental continuum and that children over 12 to 14 years of age may have near-adult capacity.[9] In the United States, however, parental permission is required for research participation by minors, with only rare exceptions.[10]

In the clinical care context, a few countries have specifically legislated the age of capacity to consent for clinical care. This legal age is often set lower than the general legal age of majority for other activities, such as voting or driving. In the absence of further legal guidance, this leaves open the question as to the type of medical interventions that are covered and, importantly, whether in these countries the same clinical legal age could apply in the context of research. Setting a legal age for consent to medical care accommodates the medical interests of minors such as their contraceptive needs and other sensitive personal health decisions in that parental authorization is not needed.[11] While this clarification is helpful, then, for minors seeking medical care, can it be "imported" into the research context?

If not legislated at a fixed age, capacity to consent for clinical decision-making can be based on this "mature minor" approach set by professional guidance or by the courts (e.g., the Gillick competency test for minors under the age of 16 in the United Kingdom if certain conditions are met).[12] Medical care legislation can also incorporate this "mature minor" rule, as is the case in Ontario, Canada, thus allowing by law for a determination of capacity to consent in the clinical context on a case-by-case basis.[13]

Recontacting Pediatric Participants

The issue of recontacting participants of pediatric research when they reach the age of majority is important for several reasons.[14] Among them, longitudinal studies and studies of large population cohorts are becoming more common. In addition, data are being stored for longer durations and increasingly shared in larger data sets. This is especially true with the recent emphasis on biobanks that collect and store (sometimes indefinitely) genomic and phenotypic data from medical records and tissue samples. Adolescents are unique stakeholders in this "recontact to consent" debate by virtue of their de facto increasing capacity to understand the risks and benefits of the research in which they are enrolled, or by virtue of being legally presumed capable of doing so at a certain age. Recontact to consent at the age of majority could be seen as the extension of the recognition that consent is a continuing process.[15] According to this principle, when participants acquire the capacity to consent, they have the right to decide either to continue taking part or to withdraw their parents' proxy consent.[16] Thus, as children mature, their assent to participate in research

should be sought,[17] and when these participants reach the age of majority, their consent should be sought as well.[18] However, this approach is attended by practical concerns, such as its viability, to say nothing of its impact on the research project.[19]

From an ethical point of view, it could also be argued that the interests in maintaining research data sets and avoiding attrition from participants cannot override the rights of research participants. Respect for persons, and for their autonomy and voluntariness, requires that informed consent be obtained. However, a more flexible approach could be that, when youths attain the capacity to give consent, their right to withdraw from research remains but formal recontact for another explicit consent to continue to participate is not required.[20]

Of note is that the 1989 *United Nations Convention on the Rights of the Child* states that the best interests of children are "a primary consideration"[21] and that children have a right to be heard.[22] The "best interests of the child principle" should guide all decisions in research and the clinic concerning minors.[23] Thus, while parents can legitimately exercise authority over their children, decisions in research and the clinic concerning minors are guided by the "best interests of child" principle. Interpretive guidance on this principle for the research setting includes language to the effect that researchers should determine whether a minor recruited for research is capable of forming an opinion, can exercise discernment, or is able to assess the material risks and benefits as well as the long-term effects of participating in research, and this in a context that permits expressing an informed decision.

As mentioned, the differing terminology, definitions, and requirements in the context of research include obtaining the assent of minors at an early age when appropriate, irrespective of the issue of legal majority. Moreover, in the last decade, there has been a conceptual shift first from parental (or legal guardian) "consent" to "authorization," then to parental "permission,"[24] and now to parental "responsibility." This is reflected in the proposed 2018 "EU Data Protection Regulation" on consent to the use of data, which holds that it "shall only be lawful if and to the extent that such consent is given or authorized by the holder of parental responsibility over the child or is given by the child in circumstances where it is treated as valid by Union or Member State Law."[25]

Longitudinal pediatric studies, pediatric clinical trials, and research with newborn screening bloodspots are research contexts that reveal the complexities of determining whether there is an ethical obligation to recontact pediatric participants when they reach the age of majority.

Notwithstanding these changes in the terms used to describe the role of parents, it bears noting that the ambit of parental authority over research or clinical decisions may be limited in certain contexts. This is exemplified in the very recent controversy on both the return of genomic research results to parents and on ensuing professional obligations. While return of results is not the focus of this paper, this controversy serves to illustrate the narrowing ambit of parental rights. Indeed, both in Europe and Canada, according to professional guidance, parents cannot refuse the return of clinically actionable results (i.e., when prevention or treatment is available during childhood).[26] Yet, in 2015, the American College of Medical Genetics and Genomics issued guidelines concerning clinical (not research) testing using next-generation sequencing that allow parents to opt out of receiving results or secondary findings concerning their child prior to undergoing genetic testing for a specific condition.[27] Later in the same year, the American Society of Human Genetics (ASHG) recommended that, "in general, parents should be able to decline to receive secondary findings in advance of genetic testing." However, it recognized that "when there is strong evidence that a secondary finding has urgent and serious implications for a child's health and welfare, and effective action can be taken to mitigate that threat," the clinician should communicate those findings to parents or guardians "regardless of the general preferences stated by the parents."[28] Adoption of this ASHG approach in the U.S. would put the country in line with Europe and Canada, whose approaches similarly limit the scope of parental authority concerning medically actionable results during childhood.

Recontact: Three Illustrative Contexts

For the purposes of our contextual analysis, we use the terms "age of majority" or "maturity" to indicate that someone has attained the status of a "competent minor," irrespective of jurisdiction. We have chosen to examine the concept of the competent minor and recontact for purpose of consent in three contexts: 1) longitudinal, pediatric cohorts that could include biobanks, 2) the "classical" pediatric clinical trial where data and samples from children may still be in use when participants become competent minors, and 3) the potential use of public health newborn screening bloodspots (traditionally collected for monogenic disorders) in research.

■ ***Longitudinal, pediatric cohorts that could include biobanks.*** Pediatric longitudinal cohort studies usually have ongoing contact with the children enrolled. For example, membership in some cohorts begins in utero or at birth. Thus, participants will be involved during different stages of their development, perhaps well beyond the age of majority. As a result, there may be more opportunity to accurately determine maturity or respect research majority where legally fixed. Some longitudinal cohorts have associated databases and biobanks that serve as resources for future research.

The LifeLines cohort study in the Netherlands (which includes a biobank), has minors who are 12 years old sign a consent form together with at least one parent. LifeLines provides opportunities for interaction between researchers and minors, and recontact has specifically been integrated into the study protocol. When participants reach the age of 18, LifeLines sends them a recontact birthday letter requesting their consent for ongoing inclusion in the adult cohort of the study.[29] The Avon Longitudinal Study of Parents and Children (ALSPAC) in the U.K.[30] is another longitudinal cohort with a biobank. It has a policy of recontacting participants when they turn 18. In a study it conducted about the recontact issue, the ALSPAC found no evidence that the communication method used to recontact participants (phone, postcard, designed packs[31]) influenced the consent decision of these "now adults."[32]

Another example is the Canadian Health Measures Survey (CHMS), under the jurisdiction of Statistics Canada. Since 2007, the CHMS has included children from age 6 years onwards, as well as adults. An unpublished report from Statistics Canada indicates that the CHMS adopted a policy of recontact for consent at age 14 years but had a nonresponse rate averaging 72% after the first contact attempt, dropping to 33% with additional recontact attempts spanning over several months. These averages are from data collected over four years. Counted as nonresponsive were those who could not be contacted and a small number who were contacted but provided no answer.

In 2011, the Office of the Privacy Commissioner (OPC) of Canada responded to a privacy impact assessment submitted by Statistics Canada. It held that the absence of an explicit consent at age 14 years, including in the event of the inability to contact, was the equivalent of no consent from the individual and should result in the destruction of that person's biospecimens and data. Attrition is a serious issue for pediatric longitudinal cohorts where childhood development is under study and participants are considered representative of the general population (i.e., not disease specific). To date, no biospecimens or data have been destroyed. There have been ongoing discussions with the OPC and the Research Ethics Board of Health Canada and with the Public Health Agency of Canada aimed at achieving a feasible approach to recontacting youth respondents while maintaining the integrity of the pediatric data. Statistics Canada agrees that the study should involve participants in their own decision-making process when they reach 14 years of age and is now adopting a recontact process with a notification and opt-out opportunity. This notification letter will explain the survey, remind participants that their parents consented for them, and tell them they can withdraw if so desired.

The Canadian Tri-Council Policy Statement[33] on ethical conduct for research involving humans mandates that "if children mature sufficiently to decide on their own behalf (subject to legal requirements), the researcher must seek the children's autonomous consent in order for their participation to continue."[34] Furthermore, it states that "when authorization for participation was granted by an authorized third party and a participant acquires or regains decision making capacity, the researcher should promptly seek the participant's consent as a condition of continuing participation."[35]

Some studies set a specific age for recontacting minor participants. For example, in Norway, children are notified at 15 years of age of their inclusion in the Norwegian Mother and Child Cohort, and consent is requested when they reach age 18.[36] For the Saudi Biobank, there is no recontact at 18 years of age, but at that age, withdrawal from research is possible: "[c]hildren will know about their participation either when they give assent personally or when their guardians notify them about participation."[37] In the U.S., some have argued that the current research regulations may not require obtaining new consent upon reaching majority if all the data have already been collected and are being managed appropriately.[38] The provisions of the Notice of Proposed Rulemaking to amend the U.S. research regulations would alter these rules, requiring consent at the age of majority to continue to collect new biospecimens.[39]

The examples from longitudinal pediatric cohorts are indicative of the patchwork of approaches currently in use around the world. As concerns biobanking activity specifically, the Recommendation 2016(6) of the Committee of Ministers of the Council of Europe holds that "where a person not able to consent . . . attains . . . the capacity to consent, reasonable efforts should be made to seek the consent of that person for continued storage and research use of his or her biological materials."[40] The guidelines the Organisation for Economic Co-operation and Development issued in 2009, "Guidelines on Human Biobanks and Genetic Research Da-

tabases,"[41] advise without further elaboration that "[t]he operators of HBGRDs involving participants who are minors or with impaired decision-making capacity should have a clearly articulated policy on what steps will be taken, in accordance with applicable law and ethical principles, once such participants become legally competent to consent."[42]

■ *Clinical trials.* Clinical trials that involve the administration of drugs, devices, or interventions during a specified period differ significantly from longitudinal research that is largely epidemiological in nature. For an ongoing clinical trial involving children or minors, a research team might be recontacting a competent minor (now mature adolescent) for the purpose of obtaining his or her consent to ongoing participation, including study-specific interventions and ongoing collection of data. Alternatively, the research team might contact a now mature adolescent in order to share a summary of the results of the research in which the individual has taken part; in this case, recontact would serve as a reminder or notification of the adolescent's ongoing involvement and may influence his or her decision to continue participation.

Some commentators contend that there is an ethical imperative to provide to all research participants, including parents and competent minors, a summary of overall research findings, whether positive or negative,[43] or at least inform them where to find such results (e.g., on a website). The ethical justifications for the offer of aggregate results are various but include affirming the value of research participation, educating participants and the public about the research process, and building trust in the research enterprise.[44] Such results may be material to an individual's decision to continue participation. Further, making such information available acknowledges the important role the participant has played in the research and disseminates accurate scientific knowledge related to the study findings.

An example of such ongoing communication of general results and its possible influence on continued participation is found in the approach of the Children's Oncology Group (COG)[45] involving clinical trials with both biological and biobanking aims. This ongoing contact led COG to require that researchers obtain consent at the age of majority (18 years) or sooner if the minor demonstrates adequate maturity to consent to continued participation in COG research.

Despite this COG example, generally, the period for recontact in the context of clinical trials is more limited than in longitudinal studies, as the studies are time limited. During that period, however, interaction between the researcher and the minor is more intense and so offers greater opportunities for the determination of maturity for recontact for consent.

■ *Newborn screening and research.* Health-related screening is defined as "[t]he presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment."[46] Today, newborn screening (NBS) is not only part of pediatric health care but is also becoming a source of biospecimens and data for research interests that go beyond quality assurance needs.[47] In some sense, storage of NBS blood spots is a form of pediatric biobanking.[48]

NBS is a public health mandate and is standard pediatric care in most industrialized countries. It is the storage or research use of NBS bloodspots without consent that attracts controversy.[49] In the U.S., when leftover blood spots are stored or to be used for research, parental permission often is now required.[50] Seeking parental permission for storage of or research on leftover bloodspots is a separate issue from the right of the asymptomatic, at-risk newborn to be identified and treated through screening programs irrespective of parental wishes.[51] Hens and colleagues maintain that "biobanks should have a policy about returning information about preventable or treatable conditions of early onset when participants are minors" and that the consent form should contain details of the policy. They go on to say that "the right of parents to receive or not to receive genetic information about their children is limited. In the rare case that information about a preventable or treatable early-onset disease is found, they should be notified regardless of their wishes, providing the findings are subject to assessment of clinical validity and utility."[52]

In 2012, the U.S. National Institutes of Health funded four projects to examine the ramifications of applying next-generation sequencing (NGS) technologies in NBS. One project, the Genome Sequence-Based Screening for Newborn Illness and Childhood Risk, also known as the BabySeq project, is randomizing babies within two cohorts, a healthy newborn cohort and an ill newborn cohort, to standard NBS or standard NBS plus NGS. In the arm that receives NGS, pathogenic variants in genes with strong evidence for causing highly penetrant childhood-onset disease, and carrier status for childhood-onset diseases, are reported back to families. The BabySeq project is studying the impact of the return of this genomic information to parents of newborns and their physicians.[53] However, there will be many unknowns, including what

happens to the communication of other results as the child matures. As is the case with most clinical trials, BabySeq has only short-term funding, although the hope is that long-term follow-up will be feasible so that this latter question, as well as others, can be addressed. Notably, in the hope that these long-term questions can be addressed with future funding, BabySeq is obtaining parental permission to recontact participating minors to obtain assent at 13 years of age and consent at 18 years.

Achieving Recontact?

Before determining the potential duties of researchers in regard to recontacting participants of pediatric research for consent at majority or maturity, we distinguished three different contexts based on the risks and benefits present in each: longitudinal studies, short-term research projects, and secondary research with newborn bloodspots. For the purposes of our discussion, we presume that withdrawal from ongoing research participation is always an option, although we recognize that anonymized or published data cannot be withdrawn. Indeed, recontact provides an opportunity to operationalize the choice to withdraw or to refuse further use of participants' data or biospecimens.

In some longitudinal research designs, contact with research participants is planned (such as for follow-up or repeat questionnaires or measurements). Other longitudinal studies keep participants informed of the evolution of the study by sending newsletters or via a website. Such studies could also foresee recontact in the original parental authorization for either the future assent of the child or (where applicable) to ask minors for their own consent when they reach majority or maturity. In some studies, permission to recontact to obtain informed consent from minors in the future could be part of the original consent, or permission to recontact could be obtained later at a convenient time, such as with repeat questionnaires or updates, thus decreasing privacy concerns. In other studies, such as biobank-related research, posting general research-project information on the Internet and making reasonable efforts to notify participants at majority that they have the option of opting out of future research could be considered sufficient. However, when active participation by the minor ceases for a significant period prior to majority or when the investigator is no longer in touch with the family, the feasibility, practicability, or costs of recontact may make it unrealistic, and obtaining a research ethics board (REB) waiver for recontact may be possible.

Most pediatric research falls in the category of "research with limited duration." While prospective consent to recontact can be obtained in short-term research, realizing such promises can nevertheless be problematic, for example, if there is lack of ongoing funding or if it is impractical or unfeasible to recontact participants. Yet when it is possible to do, it could be argued that from an ethical perspective, respect for individuals' exercise of autonomy mandates recontact. However, if research participants are to be recontacted to obtain consent at majority, it would be important to be transparent about such future recontact and inform parents during the consent process. Some research involves parents as well as their children, and parents could feel uncomfortable that their child is confronted with sensitive data.[54]

There are arguments both for and against recontact for autonomous decision-making by the research participants in this context. At present, this issue may not be well addressed in consent forms, as demonstrated in a Canadian review of pediatric research consent forms. This study revealed that 49% of a selected sample of consent forms used in a wide variety of Canadian pediatric research do not address the potential for future recontact at the legal age of majority.[55] This is contrary to the ethical norms governing research involving humans in Canada.[56] In contrast, a review of six birth cohorts in North America and Europe showed that studies that follow children past early childhood and into the adolescent years recognize a need to consider the wishes of the maturing child and to respect their autonomous choices when they attain age of legal majority.[57] Another qualitative study that involved interviewing young adults who were former pediatric oncology patients with stored research biospecimens revealed their wish (when feasible) to be asked for consent upon adulthood for continued research with their data. They did, however, consider it acceptable to continue to conduct research if participants could not be located.[58] Therefore, again, even in short-term research, it seems that an option for recontact for consent at maturity or majority should be discussed during enrollment. However, when recontact is not possible, a waiver could be sought from an REB, thus allowing ongoing use of biospecimens and data.

The use of pediatric biobanked legacy collections for secondary research often involves data or biospecimens from individuals who were enrolled as children and now may have reached majority. Presuming that no specific recontact choices were made in the original consent and in the absence of a broad consent covering future secondary research with legacy biospecimens, either all participants would have to be recontacted, or an REB waiver of recontact would have to be sought.[59] Attention should be paid to the fact that recontact can be burdensome or cause disproportionate expense and effort for researchers. The implications of

recontact on personal and familial privacy and on overall researcher obligations are unknown. Would a "secondary" researcher have any duty to recontact, notify, or obtain consent from the "now adult"? The content of the original parental consent would govern this situation, especially as concerns data-use limitations.

Conclusion

As a best practice, we suggest that researchers address recontact issues at the time of the original enrollment of children in research and clearly state what will happen, when, and why. This could include no recontact, anonymization of biospecimens and data before further research, or even destruction of data and biospecimens at the age of majority (the latter two approaches potentially compromising the scientific aims[60]). In other studies, where researchers are in dynamic and ongoing communication with their minor participants, the general rule is to ask the participant at maturity or majority for his or her consent to continued participation. At a minimum, it is reasonable to notify the individual with information concerning participation and to provide the possibility of opting out and the procedures for doing so. For now, researchers' emerging duty to recontact will inevitably be circumscribed by both the practical and principled considerations we have raised.

An obligation to recontact—a "must" about this step—is laudable and respectful of first-person consent; however, efforts to do this should be balanced with the feasibility and cost (both human and economic) entailed.[61] Although some would argue that without exception it should be mandatory that "at the age of majority the participant in principle can re-consent or withdraw his/her consent," even authors taking this position concede that in reality only a best effort can be applied.[62] The ethical acceptability of this is supported by empirical evidence that many participants are comfortable with having their data used in the event that recontact is difficult.[63]

It is important to consider the vulnerability of adolescents, the difficulties involved in finding them, the inability to judge the "reality" of presumed maturity, and the infringement of their privacy as "now adults." The risks of recontact in terms of both sociopsychological and familial impact should not be underestimated. The burdens, costs, and inefficiency of such "tracking" are very real. Is there a reasonable likelihood that such contact will make a difference? What are the risks of not recontacting? In situations where there was no ongoing communication with the individual minor, one could argue that respect for the autonomy of the presumed "now adult" could be limited to reasonable efforts to notify or remind parents (on websites or by letters) to tell their "now adults" that they were enrolled in research. Again, the costs and effectiveness of such an approach merit evaluation.

Overall, we maintain that the anticipated benefits of recontact should outweigh the risks and that the decision to recontact should be proportionate to the specific context, the nature of the research, and the best interests and expectations of the then minors and their families when the individuals were first enrolled even though they are now adults.

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BY KEMNIQUE RAMNATH, SARITA CHEAVES, LISA BUCHANAN, KRISTINA BORROR, AND MARINNA BANKS-SHIELDS

Incident Reports and Corrective Actions Received by OHRP

In this article, we describe our review of incident reports and the corrective actions included in those reports that the Office for Human Research Protections (OHRP) received between January 1, 2008, and December 31, 2014. OHRP is the division of the Department of Health and Human Services (HHS) responsible for overseeing compliance with the HHS regulations governing research with human subjects.[1] The regulations require institutions that conduct research under an OHRP-approved assurance to have written procedures to ensure that incidents related to regulatory requirements are promptly reported to OHRP.[2] These incidents include 1) any unanticipated problems involving risks to subjects or others, 2) any serious or continuing noncompliance with this policy or the requirements or determinations of the institutional review board (IRB), and 3) any suspension or termination of IRB approval. After receiving, processing, and reviewing an incident report, OHRP responds to the institution in writing, typically by email, generally confirming that the report was adequate, seeking additional information about the reported incident, or recommending or requiring that the institution enact additional corrective actions.

When reviewing an incident report, OHRP assesses most closely the adequacy of the actions taken by the institution to address the incident. Specifically, OHRP assesses whether the corrective actions will help ensure that the incident will not happen again with the investigator or protocol in question, with any other investigator or protocol, or with the IRB. Therefore, OHRP recommends that, when appropriate, corrective actions be applied to the entire institution. Corrective actions, as defined by OHRP, are those activities that an institution implements when it is trying to resolve an issue that resulted in regulatory noncompliance in its human research protections program or to address other problems in research. These corrective actions can be either self-imposed by the institution or mandated by OHRP. Corrective actions have been key in rectifying the systematic problems that institutions encounter related to protecting human subjects in research and complying with the HHS regulations.

This review of incident reports and corrective actions as stated in those incident reports from 2008 to 2014 will examine the most prevalent incidents reported and corrective actions implemented by institutions and discuss the limitations of the data and best practices for institutions. The overwhelming majority of the institutions at which reported incidents occurred were domestic (97.8%, or 818 out of 836 institutions). The institutions that submitted the reports include domestic and international public and private universities and colleges, private research institutions, IRBs, medical schools, academic medical centers, community hospitals, and federal health care and research facilities.

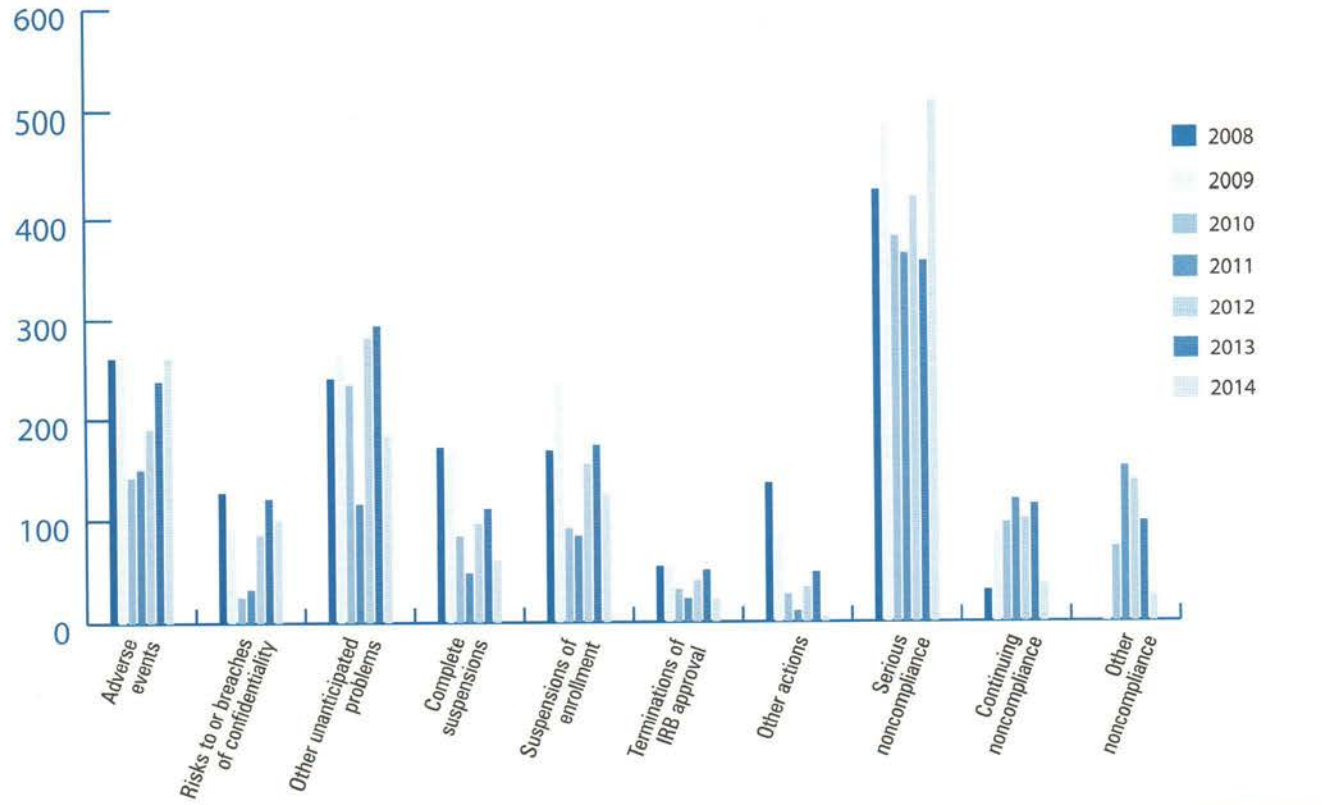
Key Findings

Between January 1, 2008, and December 31, 2014, OHRP processed 6,511 incident reports from 780 institutions. The numbers of incident reports received by OHRP each year were as follows: 827 in 2008, 1,105 in 2009, 955 in 2010, 913 in 2011, 885 in 2012, 827 in 2013, and 999 in 2014. Many of the incident reports received and processed contained more than one incident; in total, then, these 6,511 incident reports documented 8,570 incidents.

Figure 1 shows the types of incidents reported to OHRP between January 1, 2008, and December 31, 2014. These include 1,506 adverse events (including unanticipated ones), 582 risks to or breaches of confidentiality, 1,556 other unanticipated problems, 734 complete suspensions of IRB approval, 1,030 suspensions of enrollment of new subjects, 274 termi-

Ramnath K, Cheaves S, Buchanan L, et al. Incident reports and corrective actions received by OHRP. *IRB: Ethics & Human Research* 2016;38(6):10-15.

Figure 1.
Types of Incidents Reported to OHRP

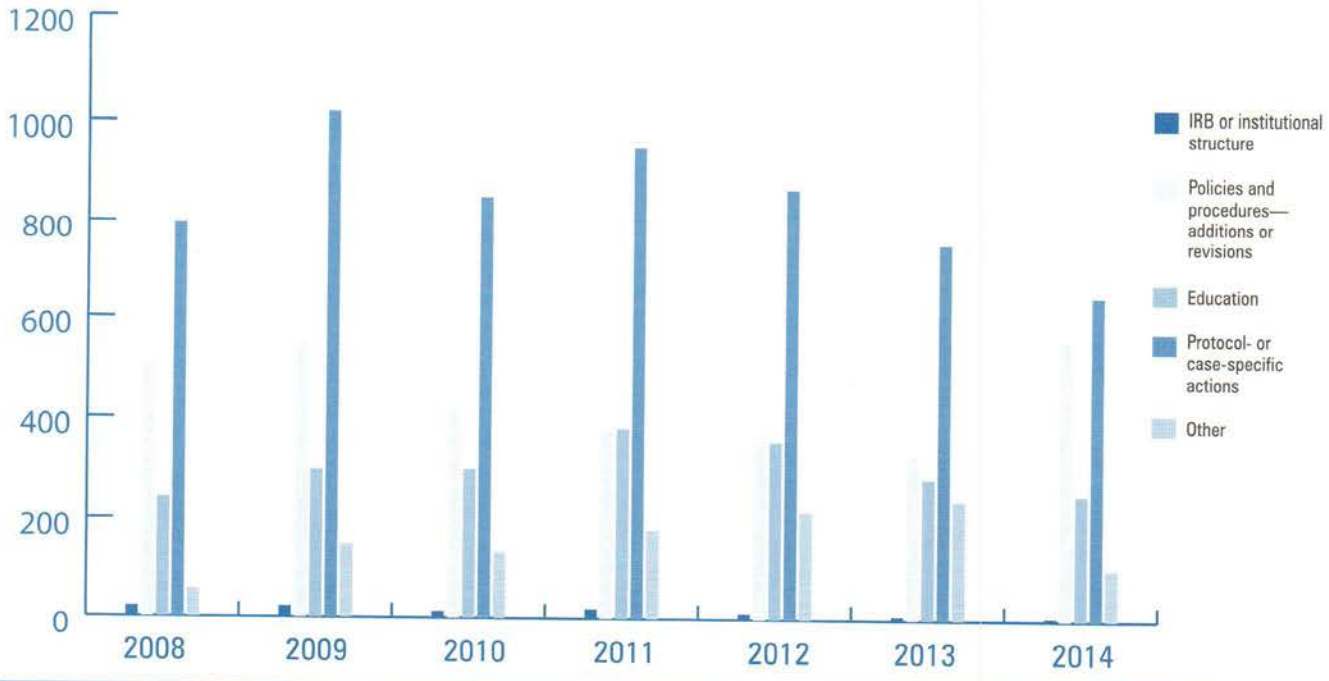


nations of IRB approval, 344 other IRB actions, 2,943 instances of serious noncompliance, and 583 instances of continuing noncompliance. Examples of other unanticipated problems included events such as research participants' receiving the wrong dose of a study drug or the wrong drug but having no ill effects, a study's enrolling ineligible subjects, and subjects' threatening research staff. "Other IRB actions" include notifying a sponsor or regulatory authorities of the event. Note that a single event may be counted as two (or three) different incidents: for example, noncompliance could also represent an unanticipated problem, which could lead to a suspension of IRB approval. There is some fluctuation between years in the numbers of each type of incident being reported. OHRP received the most incident reports in 2009.

Figure 2 (available via the *IRB: Ethics & Human Research* web page) shows the 10 most common areas of serious and continuing noncompliance that were reported to OHRP from 2008 to 2014. Serious noncompliance was the most common type of incident, with 2,943 instances (data not shown). Approximately 51% of that noncompliance related to protocol changes without IRB review and approval (1,515 instances). Another category of serious noncompliance involves informed consent issues; 970 such incidents were reported to OHRP during this time period (33% of the instances of serious noncompliance). These were the top two categories of serious noncompliance and continuing noncompliance. Protocol changes without IRB review and approval that were reported to OHRP included study interventions not administered as required by protocol, compensating subjects more than allowed in the protocol, and failure to follow inclusion or exclusion criteria. Noncompliance related to informed consent included failure to obtain informed consent prior to inclusion in research, failure of the informed consent document to include all the risks of the research, and failure of the subject to sign the consent form prior to participation in research.

Between January 1, 2008, and December 31, 2014, OHRP received reports of a total of 12,326 correc-

Figure 3.
Total Number of Corrective Actions Reported to OHRP



tive actions distributed in six major categories from 836 institutions. The categories include 52 individual subcategories of corrective actions. Figure 3 shows the total number of corrective actions reported to OHRP between January 1, 2008, and December 31, 2014, in each of the five major categories: changes in IRB or institutional structure; addition or revision of IRB policies and procedures; education of investigators, research staff members, IRB members or staff members; protocol- or case-specific actions; and other corrective actions. A sixth major category, revisions of IRB application forms, was not included in the chart due to the low number of corrective actions in this category (13 between 2008 and 2014).

Protocol- or case-specific corrective actions comprise the largest category of corrective actions and are those that involve an action related to a particular study or studies (with 5,905 instances reported). Some of the subcategories in this category include re-review of protocol(s) or grants by an IRB, submitting subpart C certifications to OHRP (for research involving prisoners, certifying that the IRB has made certain findings regarding the research), suspension of the investigator, termination or replacement of the principal investigator or another research staff member, monitoring or auditing of the investigator, training of the principal investigator on specific issues, requiring the principal investigator to submit amendments to the protocol, requiring the principal investigator to revise consent forms for specific studies, requiring the principal investigator to obtain additional research staff, terminating the protocol, suspending or revoking the investigators' privileges to conduct human subjects research, disallowing the use of data or attaching conditions to its use, and requiring reconsent or notification of subjects.

Instances of adding or revising policies and procedures comprise the second-largest category of corrective actions (with 3,098 instances reported). They include revision or addition of the following: initial review procedures; continuing review procedures; procedures regarding reporting unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspending or terminating IRB approval; contingent approval procedures; IRB reviewer checklists (informed consent; expedited reviewer; subpart B, C, or D; waiver of informed consent; and waiver of documentation of informed consent); expedited review procedures, procedures for review of proposed changes to research, minute recording, and documentation of IRB findings or actions; electronic

tracking of protocols or development of the electronic IRB record; procedures for determining exemptions; subpart reviews; auditing programs; procedures for conducting investigations; and research standard operating procedures.

Educational corrective actions involve the education of investigators and research staff members or all investigators at the institution, IRB members or staff members, or institutional officials. OHRP received reports of 2,114 instances of corrective actions involving education from 2008 to 2014.

"Other" corrective actions are those that did not fit into the five other major categories (with 1,091 instances reported). Some of the subcategories under other corrective actions include disallowing use of data, mentoring or supervision of a researcher, and other case-by-case specific corrective actions (e.g., investigation by a safety monitoring board, providing a subject with treatment for an adverse event, or obtaining a Certificate of Confidentiality for the study). Corrective actions involving revisions of IRB application forms include soliciting information on informed consent, soliciting information on subpart D of the regulations (research involving children) or other subparts, soliciting information on other vulnerable populations, and soliciting information on criteria of approval of research.[3] There were only 13 such corrective actions reported to OHRP from 2008 to 2014.

IRB or institutional structure corrective actions included restructuring the IRB, adding staff members or making staffing changes, adding an IRB(s), changing the signatory official, changing the official or office to which the IRB reports, and adding a research compliance officer or office.

Figure 4 (available via the *IRB: Ethics & Human Research* web page) shows the top 15 subcategories of corrective actions reported to OHRP between January 1, 2008, and December 31, 2014, and the percentage of the total. A total of 12,326 corrective actions were reported to OHRP from 2008 to 2014. The most common corrective action subcategory was addition or revision of research standard operating procedures, which falls under the category of policies and procedures (2,551 instances). Examples of this include the implementation of encryption protocols for institution research laptops and flash drives, the use of checklists to confirm conduct of study procedures, and the revision of a mechanism to notify the research team of lab data. Education of investigators or research staff members was the second most common, at 1,779. The third most common corrective action was to have subjects reconsent or to notify them.

The category "addition or revision of policies and procedures" also included (but is not limited to) corrective actions revising policies and procedures involving implementation of auditing program(s) (196) and electronic tracking of protocols or development of the electronic IRB record (61). In the "protocol or case-specific changes" category, the following corrective actions are also included: reconsent or notify subjects (1,206), require the principal investigator (PI) to submit an amendment or to amend the protocol (1,071), require the PI to revise consent forms for specific studies or to amend consent (760), use of data disallowed or conditions attached (439), training of the PI on specific issues (289), re-review of protocol(s) or grants by the IRB (242), and the PI's obtaining additional research staff (227). Corrective actions related to training or educating also include education of investigators and research staff members (1,779), education of all investigators at an institution (188), and education of IRB members or staff members (131).

Institutions often fear that reporting incidents to OHRP will be a "red flag" of concern for the agency. Indeed, the opposite is the case: OHRP is more concerned about institutions that do not report, as we recognize that incidents do occur, despite the best intentions of all involved.

Each year, the numbers for the corrective actions reported to OHRP in incident reports remained relatively the same for each category. From 2008 to 2014, the protocol or case-specific changes category led in numbers, while revision of IRB application forms consistently had the fewest instances reported, with an average of 3 reported per year (data not shown).

To estimate the percentage of incident reports for which OHRP requests additional information, we analyzed the number of times OHRP did so in 2013 and 2014. OHRP received 1,826 reports in 2013 and 2014 and requested additional information 69 times. Therefore, only approximately 3.8% of the time did OHRP request additional information. The information requested was usually a final report on the matter. OHRP may request that any corrective actions taken

will be ones that help prevent a particular noncompliance problem from reoccurring at that institution.

Discussion

The data presented here have certain limitations. For example, the number of incident reports processed from 2008 to 2014 is greater than what is presented. Multiple reports were sometimes logged in one entry in the Compliance Activity Tracking System. Reasons for this include that 1) multiple reports are sent from one institution at one time, 2) the principal investigator is the same for several protocols, 3) the reports received from an institution include multiple incidents that are in the same category of noncompliance, and 4) the reports received from an institution include multiple incidents that are for the same protocol. This means that the actual number of incidents reported is also greater since multiple reports are processed in one entry.

As noted above, more incidents were reported in 2009 than any other year described in this analysis, particularly, adverse events, suspensions of new enrollments, and serious noncompliance. It is not clear why there were more such incidents reported that year than other years. We note that OHRP issued several final and draft guidance documents during this time (including guidance on continuing review of research and on IRB "Approval of Research with Conditions") but none dealing with reporting of incidents to OHRP. OHRP issued "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" in 2007[4]; it is conceivable that institutions took two years to implement this guidance, but it seems unlikely. OHRP issued guidance on compliance oversight procedures in 2009,[5] but this guidance does not describe incident reporting. Another possibility is the increased number of quality assurance workshops that OHRP conducted in the previous year (10 in 2008, compared to an average of 6 in other years). These workshops often include training on reporting to OHRP. We also do not know if there were more actual events in 2009 than in other years or whether the rate of reporting was higher.

Another limitation is that the corrective actions examined represent only quantified data for each action taken by institutions that is reported to OHRP. As indicated above, OHRP received a total of 12,326 corrective actions distributed in six major categories between 2008 and 2014. The data do not show the fact that institutions often implement multiple corrective actions per incident. In addition, no follow-up data are available to assess the effectiveness of the actions to remedy systemic problems. When institutions report incidents to OHRP, each incident may have multiple corrective actions, or a single corrective action may address multiple incidents. Thus, there is not a one-to-one correlation between incidents and corrective actions, and OHRP does not track correlation between these. This should be kept in mind when reviewing the data.

Another limitation of the data presented here is that institutions might implement corrective actions but not report them to OHRP. In addition, the kinds of activities represented by corrective actions may be undertaken independently of any incident at all. For example, an annual review of policies and procedures might lead the institution to revise several policies and procedures, and institutions may educate investigators and staff members as part of a regular annual program.

Our analysis of reported corrective actions demonstrates that the largest numbers of corrective actions relate to the conduct of research, rather than IRB processes. This is seen in the top three subcategories of corrective actions reported: addition or revision of research standard operating procedures, education of investigators and research staff members, and monitoring or auditing of a principal investigator or a research study or studies.

This analysis of incident reports may help institutions in identifying major areas of problems that need to be reported to OHRP. Institutions may wish to audit their records to ensure that such events are being adequately reported. This data analysis can also prove useful in identifying the types of noncompliance that are most frequent at reporting institutions. Awareness of this can help in targeting the root cause of the incidents and what steps should be taken to prevent further incidents. Institutions often fear that reporting incidents to OHRP will be a "red flag" of concern for OHRP. Indeed, the opposite is the case: OHRP is more concerned about institutions that do not report, as we recognize that incidents do occur, despite the best intentions of all involved. For example, low numbers of reports to OHRP are sometimes a factor in OHRP's decision to conduct a not-for-cause evaluation.

The conduct of human subjects research can be complicated and not necessarily under the control of the IRB. During the conduct of research, it is not uncommon to find that, for one reason or another, the research must be suspended or terminated or the

approved protocol has not been followed—that there is noncompliance or unanticipated problems that may need to be reported to the IRB, institutional officials, sponsors, and federal agencies. These occurrences or deviations can have a range of possible impacts depending on multiple factors such as the overall risk of the study and the nature and extent of the incident(s). Once the causes of the problem are discovered, they must be assessed, and action must be taken to correct them and prevent such occurrences in the future.

Observers of enforcement of the human subjects protections system sometimes focus their attention on findings of noncompliance in cases of investigations by the Division of Compliance Oversight in OHRP. From 2008 to 2014, there were 129 such findings made by the division. The incidents reported here indicate that there is another enforcement function that is actively in operation in the current system, one that depends on the self-governing activity of research institutions and IRBs. Of course, the two functions may be interrelated insofar as one of the incentives for self-reporting of incidents is to avoid the possibility of a compliance case investigation by OHRP. However, it is also true that many institutions may self-report incidents because they appreciate that this is a legitimate feature of the current system. In any case, looking at incident reporting as well as compliance investigations provides a more complete picture of the regulatory enforcement in the current system. OHRP plans to conduct another analysis of determinations of noncompliance found in OHRP investigations in the near future.

The authors hope that this evaluation of corrective actions reported to our office in incident reports will help institutions formulate appropriate corrective action plans when addressing noncompliance, unanticipated problems, and suspensions and terminations that occur in research conducted by investigators. This report should also highlight the areas in which problems are most likely to occur so that institutions and federal agencies can better target educational programs to help prevent those problems. For example, since protocol changes and informed consent issues have been the most frequent types of serious noncompliance, it might make sense to focus some educational efforts in these two areas. We also note that educational efforts are a common form of corrective action, and so institutions should be prepared to design and conduct educational activities in response to anticipated incidents.

Figures

Figures 2 and 4 are available via the *IRB: Ethics & Human Research* web page, part of The Hastings Center website.

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2016 Index
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