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Preserving and Enhancing the Responsible Conduct of Research Involving Children and Youth

A Response to Proposed Changes in Federal Regulations

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Abstract

For the first time in twenty years the U.S. Department of Health and Human Services (DHHS, 2009) is considering changes to federal regulations governing research. The Common Rule provides the basis for government regulations and Institutional Review Boards (IRB). Proposed changes will have a significant impact on Institutional Review Board evaluation of research involving infants, children and adolescents. For example, such a revision can serve to rectify or exacerbate often observed IRB inconsistencies and over-estimation of probable harms when applying "minimal risk" or "exempt" criteria to research involving minors. Proposed revisions may also affect the feasibility of research on adolescent risk that requires waiver of parental or guardian permission to be successfully implemented. Further, recommendations for a new category of "informational risk" based on current and emerging advances in analysis and storage of bio-specimens and information technologies for archival research will have significant influence on ethical procedures required for collection and storage of longitudinal and cross-sectional data. Given the importance of any rule change to the conduct of science related to children, the Society for Research in Child Development (SRCD) convened the SRCD Task Force on Proposed Changes to the Common Rule. The purpose of this report is to alert policymakers, scientists, and participant groups to proposed changes most relevant to research involving children and to provide recommendations for ensuring the responsible conduct of child and adolescent research in the final regulatory changes.

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From the Editors

One of the consistent and predictable phenomena in developmental and behavioral science is the verbal expression of dismay, often accompanied by much negative affect, when the term "IRB" enters a conversation among colleagues. In their work with participants, most researchers understand and adhere to the values of respect, beneficence, and justice, which are the foundations of the ethical practice and the regulations created by the Department of Health and Human Services (DHHS) to govern research with human participants. In this issue, Fisher et al. note that the DHHS federal regulations, which emerged from the Belmont Report and are specified in the Common Rule, were originally created with biomedical research in mind. The application of those guidelines to social and behavioral research has created barriers to conducting research with children and youth, sometimes resulting in, as the authors note, "therapeutic orphans" (i.e., individuals from vulnerable populations who cannot benefit from the results of research because of limitations to their participation).

The world has changed in the 20 years since DHHS published the last set of federal guidelines, and the agency has now proposed changes to the Common Rule guidelines and posted them for comment. The Society for Research on Child Development established a committee of experts, led by Celia Fisher, to review the changes and comment on the revisions. In this report, Fisher and group summarize the comments and rationales shared with the DHHS and in doing so, alert researchers to changes that could facilitate research conducted with children and youth. Among the issues they address are: the concept of minimal risk and an age-indexed, general population risk definition; polices for streamlining research that has little or no risk (e.g., common educational practices); improvement in the form of informed consent to enhance understanding of research participation; removing statements about institutional liability from description of risk; revised definition of emancipated minor and situations in which guardian permission might be waived; and uses and security related to data sharing and data repositories.

In his commentary, Pimple, an applied ethicist, agrees with most of the responses of the SRCD Committee to DHHS. He offers additional recommendations related to reactive wording in consent forms in the new proposed regulations, proposes holding firm to the prohibition of re-identifying individuals who have contributed "de-identified" data, and importantly, distinguishes between the concepts of harm and justice as applied to vulnerable populations and its implication for the statement of regulations. In their commentary, Yazijan and Goldman, developmental scientists, also commend the SRCD committee on their close inspection of the changes. They reiterate the point that the current IRB process has been based on a biomedical model and is ill-fitted for social and behavioral research. They note that parents, child and youth participants, at time, cannot understand IRB-required consent forms and urge revisions that allow for modification of the consenting process.

In conclusion, Fisher and the SRCD committee do a great service for the field by reviewing closely the proposed changes in regulations and providing constructive recommendations to DHHS. Ultimately, such changes may well align with those core values of respect, beneficence, and justice that guide us as a community of researchers and policymakers.

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Preserving and Enhancing the Responsible Conduct of Research Involving Children and Youth

A Response to Proposed Changes in Federal Regulations

For the first time in twenty years the U.S. Department of Health and Human Services (DHHS, 2009) is considering changes to the Common Rule section of federal regulations governing research involving human participants. Requests for public comment on proposed changes appeared in the 2011 *Federal Register* (DHHS, 2011) Advance Notice of Proposed Rulemaking (ANPRM). The Common Rule plays an integral role in government regulations and Institutional Review Board (IRB) evaluation of research involving infants, children and adolescents. However, neither the ANPRM nor the majority of public comments thus far have addressed the effects of proposed rule changes on research involving this critical participant group.

Given the importance of any rule change to the conduct of science related to children, in August, 2012, the Society for Research in Child Development (SRCD) convened the SRCD Task Force on Proposed Changes to the Common Rule. Drawing on the work of the Task Force, the purpose of this report is to alert policymakers, scientists, and participant groups to proposed changes most relevant to research involving children[1] and to provide recommendations for ensuring the responsible conduct of child and adolescent research in the final regulatory changes.

A Brief History

Known as the Common Rule, 45 CFR 46 Subpart A provides the fundamental procedures IRBs must follow to provide the government with assurances that their institution is protecting the rights and welfare of individuals participating in research. The Common Rule language does not distinguish among types of participant populations and includes only a general reference to children as one of several vulnerable populations requiring additional protections (§46.111[3]). Specific additional protections for research involving minors were codified in 1983 as Subpart D *Additional Protections for Children Involved as Subjects in Research*.

During the 30 years since its adoption, Subpart D has helped investigators and IRBs appropriately balance research participation protections and the pursuit of scientific knowledge to advance children's welfare. However, investigators conducting research involving these populations and IRB review of child relevant research protocols must comply with all of the requirements of both Subparts A and D http://answers.hhs.gov/ohrp/categories/1562. For example, although "minimal risk" is a key concept under Subpart D regulations determining the types of research involving children IRBs can approve (§§46.404–407), the definition of "minimal risk" only appears in the Common Rule (§46.116). Regulations within the Common Rule also establish whether research involving children is exempt from or can undergo expedited IRB review (§§46.101 and 110) as well as criteria for confidentiality protections (§46.111a[7]). Finally, rules relevant to waiver of parental permission under Subpart D (§46.408) are specifically linked to Common Rule §46.116. It is therefore essential to the success of the rule-change process that clear and specific consideration be given to how proposed Common Rule changes will affect implementation of Subpart D.

Estimates of Research Vulnerability and Children as Research Orphans

Pediatric and development scientists often encounter roadblocks to the conduct of scientifically valid and socially valuable research as a result of IRB risk/benefit assessments that over-estimate participant risk and risk protections required (Shah, Whittle, Wilfond, Gensler, & Wendler, 2004). IRB decisions are often motivated by

[1]Consistent with regulatory language, throughout this report the terms "child", "children" and "minor(s)" represent the broad category of participants from infancy through adolescence. The term "adolescent" is used in sections uniquely relevant to that developmental period.

value-laden concepts of vulnerability in areas such as adolescent sexuality research, resulting in institutional barriers to the quality and conduct of socially critical research that has the potential to improve the health and welfare of childen and youth (Mustanski, 2011; Wendler, Belsky, Thompson, & Emanuel, 2005). One reason for this over-protective IRB stance is that Common Rule regulation §46.111a[3] refers to children as a "vulnerable" population requiring additional protections—but the regulation neither defines vulnerability nor references the additional protections provided in Subpart D. As a result, in practice some IRBs develop their own definitions and practices for what constitutes additional protections rather than basing their protection requirements on Subpart D. In some cases, paternalistic protections that discourage research involving children create a population of "therapeutic orphans," unable to accrue the benefits derived from scientific advances (Leonard et al., 1996). We believe Subpart D includes sufficient provisions for protecting the rights and welfare of child populations and recommend that Common Rule §46.111a[3] clearly state that children as a class, especially adolescents, should not by default be considered "vulnerable" to research when protections dictated by Subpart D are met. Rather, as with adults, IRBs should be directed to define vulnerable child populations in terms of special needs for protections that may arise from medical illness; physical, emotional or intellectual disability; or unsafe environments, including children who may be abused, homeless or living in war-torn countries.

Goals of This Report

The laudable goal of proposed changes to the Common Rule is to enhance participant protections and reduce institutional review board (IRB) and investigator burden, delay and ambivalence (Emanuel & Menikoff, 2011). We strongly support these aims and have written this report to ensure a strong voice for science related to children is included in the final rule change deliberations. Drawing on the Belmont Principles of beneficence, respect and justice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1977), our comments reflect a view of research as a moral endeavor that seeks to ensure that the welfare, autonomy and privacy rights of infant, child and adolescent research participants are adequately protected and that such protections do not prevent them from equitable sharing of the burdens and benefits of research. While there are many proposed changes in the ANPRM that have implications for research involving children, this Report focuses on four aspects with major implications for the responsible conduct of pediatric and developmental science: Minimal risk, expedited review, information risk and informed consent.

Ensuring Risk Based Protections: Defining Minimal Risk Research

Recognizing the critical role of the Common Rule definition of minimal risk in numerous provisions of 45 CFR 46, the ANPRM asked for public comment on whether the current definition "is appropriate" and "if not, how should it be changed?" (p. 44517). Any modification to the definition will have significant implications for the application of Subpart D to the conduct of health, educational and social-behavioral research involving children. For example, Under Subpart D the Common Rule minimal risk definition determines the conditions under which IRBs can approve: Research with no prospect of direct benefit to child participants; non-therapeutic research presenting a "minor increase over minimal risk"; and research involving greater than minimal risk but presenting the prospect of direct benefit to individual child participants (§§46.404-406). In addition, the minimal risk definition anchors IRB approval of a subset of waivers for parental permission and child assent (§46.408).

Interpreting and Clarifying the Definitions of Minimal Risk

According to the current Common Rule definition, "minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests" (§46.102i). Since the Belmont Report (1979), federal committees and IRBs have struggled over whether the terms "daily life" and "routine physical or psychology examination or tests" when applied to children should be indexed against a *general population* standard based on the level of risk to which healthy children living in safe environments are typically exposed or a *relative* standard requiring interpretation based on the type of risk to which the specific class of *research subjects* are typically exposed (Fisher, Kornetsky & Prentice, 2007; Institute of Medicine of the National Academy [IOM], 2004; Kopelman, 2004; National Human Research Protections Advisory Committee [NHRPAC], 2001).

Although the National Commission recommended a general population standard as preferable for pediatric research, in response to public comment, the preamble to the Common Rule articulated a relative standard describing minimal risk as "those risks encountered in the daily lives of the subjects of the research." Reflecting the continued disagreement over a relative definition for adult participants that might not be appropriate for children, the final regulatory definition included neither the "general population" nor the "subjects of the research" language, resulting in an ongoing confusion about the intent of the regulation.

The ambiguity of regulatory language in the Common Rule definition has caused wide spread inconsistency in IRB application of these regulations to pediatric protocols (Hoagwood, Jensen, & Fisher, 1996). Such inconsistencies can result in perceived or actual inequities in participant protections for children across different regions of the country, under-protection of child participants with disorders or conditions, or exclusion of children from research that may yield knowledge that can help improve child health or alleviate childhood disorders (Fisher et al., 2007; Mustanski, 2011). Examples abound in investigator reports of adolescent research involving sexuality, drug use and other health relevant behaviors in which IRBs create research implementation barriers based on the empirically unsupported assumption that surveys or interviews on such topics may harm adolescents or encourage them to engage in such behaviors (Fendrich, Lippert, & Johnson, 2007; Fisher, 2002, 2003; Langhinrichsen-Rohling, Arata, O'Brien, Bowers, & Klibert, 2006).

An Age-Indexed, General Population Definition of Minimal Risk

As scientists concerned with the protection of children's research rights and welfare, we strongly urge DHHS to adopt the general population standard to ensure that children as well as adults with health problems or living in unsafe environments will not be unjustly permitted to be exposed to higher levels of risk than healthy individuals living in safe environments (Fisher et al., 2007). On the other hand, this definition must not be so restrictive that it precludes the essential flexibility of IRBs to consider evaluating minimal risk against age-indexed risks in daily life and routine examinations (NHRPAC, 2001; IOM, 2004). For example, routine medical and psychological procedures involving preschool and school age children include blood draws, screening for mental health problems, indications of abuse or neglect as well as tests to assess cognitive, social, academic, behavioral and emotional functioning. Questions about substance use, depression, and sexuality are part of routine medical and psychological examinations for children beginning in early adolescence (Secretary's Advisory Committee for Human Research Protections [SACHRP], 2005). Furthermore, adoption of the general population standard should not prevent IRBs from determining that in some cases, risks to which the general population of children are routinely exposed (e.g., blood drawing procedures) may pose the likelihood of harms greater than minimal risk for some populations (e.g., children with hemophilia) (Fisher et al., 2007; SACHRP, 2005).

> … we recommend federal regulations adopt the following definition: Minimal risk means that the probability and magnitude of harm or discomfort introduced solely by the research are not greater in and of themselves than those ordinarily encountered in the age-indexed daily life of the general population or during the performance of routine medical, psychological, or educational examinations or tests.

We also urge that any modifications to the definition of minimal risk recognize that research involving children and adolescents is often conducted in or for schools. For such research the reference to routine medical or psychological examinations or tests in the current minimal risk definition is not sufficient and should be expanded to include educational contexts. For all these reasons we recommend federal regulations adopt the following definition: *Minimal risk means that the probability and magnitude of harm or discomfort introduced solely by the research are not greater in*

and of themselves than those ordinarily encountered in the age-indexed daily life of the general population or during the performance of routine medical, psychological, or educational examinations or tests.

Ensuring Equity in Streamlined Review of Research Involving Children: Categories of Expedited Review

Under the Common Rule, IRB review can be expedited (approved by the IRB chair or a designated member without full board review) if research presents no more than minimal risk. The Office of Human Research Protections (OHRP) provides a number of broadly worded examples of minimal risk as illustrations of research that can undergo expedited review (http://www.hhs.gov/ohrp/policy/expedited98.html). However, this list has not be updated since 1998 and IRBs are often reluctant to expedite review of minimal risk research that are not specifically listed, and frequently fail to apply the current general categories to children's research. Notably, this is the case despite the regulatory language in part B of the Categories of Research that states that except as specifically noted "the categories apply regardless of the age of subjects."

Inclusion of Age-Indexed Examples in Categories for Expedited Review

Responding to widespread dissatisfaction with the expedited review process, the ANPRM is proposing to (a) expand the category list for expedited review, (b) provide a default presumption in the regulations that a study which includes only activities on the list is a minimal risk study, and (c) eliminate the requirement of routine annual continuing review of research that has been approved under the expedited procedure. We concur with these proposals and strongly recommend that age-indexed procedures from biomedical, educational and social-behavioral research are included in any expanded expedited category list so that pediatric, educational, and developmental science receives equitable consideration in IRB review. The ANPRM is also considering a standing Federal panel to periodically review and update the list, based on a systematic, empirical assessment of the levels of risk. We concur with this recommendation and urge OHRP to ensure that this panel includes members with expertise in the application of human subjects protections to research involving infants, children and adolescents across health, educational, and community contexts.

Risk equivalence. We applaud the ANPRM proposed expansion of the expedited minimal risk category list. However, no list can adequately include all the variations in and age appropriateness of research procedures that meet minimal risk criteria. We recommend that the types of research listed in the expedited category be framed as *examples* rather than an exhaustive limited set of procedures. To be effective, the expanded category list should explicitly state that IRBs should consider as minimal risk any procedures not specifically listed in the expedited categories whose risk can be determined to be equivalent or less than the examples.

Drawing on earlier recommendations (IOM, 2004; SACHRP, 2005) we suggest that criteria for risk equivalence should be based on: (a) age appropriate experiences of the general population from which research participants will be drawn; (b) the duration and frequency of the procedure; (c) the cumulative risk posed by a set of procedures that might individually be equivalent but cumulatively be greater in probability or magnitude of risk than those in daily life or routine examinations, and (d) the degree to which any harms if they do occur are transient and reversible. In addition, to ensure equal protection and opportunities for participation for all populations, equivalent risk evaluations should not be based solely on the content area covered by an examination or test (e.g., health behaviors), but on whether the content, method and language of inquiry are age appropriate and whether the investigator has the training and has designed a protocol that can successfully implement age appropriate risk protection procedures .

Risk minimization. Pediatric and developmental scientists often face barriers to expedited review when IRBs overestimate risk by focusing on all possible harms that might arise from a breach of confidentiality rather than following regulatory language on the DHHS website, which directs IRBs to accept for expedited review protocols that include "reasonable and adequate [investigator-implemented] protections" that would ensure that "risks related to invasion of privacy and breach of confidentiality are no greater than minimal." Failure to consider the adequacy of procedures protecting confidentiality creates barriers to expedited review especially for adult and adolescent research populations engaged in illegal, health compromising, or socially stigmatized behaviors. We recommend that this regulatory language be incorporated directly into Common Rule §46.101.

ANPRM Recommendations on Streamlining Procedures for Exempt Research

We applaud the ANPRM's recommendation to address the ambiguity of language, clarify categories, and streamline the current process for exempt review. Exempt categories listed under §46.401 of the Common Rule include research involving "normal" educational practices, survey and interview procedures and other methods used in child and adolescent research. However, Subpart D does not include a specific section on exempt research. Rather the regulation state that exemptions at §46.101 of the Common Rule are applicable to Subpart D. Therefore, any modifications to this category must consider the consequences for pediatric and developmental research. For example, currently there is considerable IRB variability and investigator confusion over application of exempt categories described in §46.101b(1) and 101b(2) for research involving children conducted in "established or commonly accepted educational settings, involving normal educational practices …" and "involving the use of educational tests."

The ANPRM suggests replacing the exempt category with a streamlined excused/registered process. This change would eliminate the current requirement for exempt research to undergo IRB review. Under the new process researchers would file a brief registration form with their institution and would be permitted to commence their research studies immediately after filing the form. To reduce the possibility of over- or under-inclusion of research involving infants, children and adolescents in this new category we strongly recommend that any rule change include a description of "categories of excused/registered research" similar to the modifications recommended for the categories for expedited review, and include empirically based, age-graded and context specific examples. A standing committee charged with reviewing, expanding and modifying these categories should include members with expertise in application of research protections to biomedical, social-behavioral, and educational research from infancy through adolescence. The ANPRM has also suggested removing IRB oversight for its new excused/registered category. However, the description of an appropriate oversight mechanism remains vague. In the absence of specific and effective strategies to ensure investigator knowledge of and compliance with criteria for excused status, we believe a streamlined IRB review remains the best participant protection against decisions contaminated by investigator ignorance or conflict of interest.

Strengthening Data Protections to Minimize Information Risks

Researchers protect the privacy and dignity of persons through implementation of appropriate data security procedures. Common Rule regulations flowing from the Belmont principles of respect and beneficence require IRBs to ensure that each research plan includes "adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data" (§46.111a[7]). Data security procedures are required to avoid instances in which "identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing." (http://www.hhs.gov/ohrp/policy/expedited98.html).

Adopting the Health Insurance Portability and Accountability Act (HIPAA)

One of the proposed ANPRM recommendations is to require research involving collection and use of identifiable data to adhere to data security standards modeled on the HIPAA Security Rule. HIPAA was developed to protect informational security of and provide patients greater access to protected health information (PHI) defined as information on a patient's past, present or future physical or mental health care or payment for health care (http://www.hhs.gov/ocr/hipaa/finalreg.html). Among other requirements, HIPAA provides definitions of "identifiable" information, standards for determining adequate de-identification of information, with whom and under what conditions PHI can be shared, the rights of patients to access and appeal information within their health records, and requirements for staff training. Currently HIPAA rules only apply to researchers if: (a) they or their organization are a "covered entity" (i.e., a health care provider, health plan, or health care clearing house that transmits any type of PHI electronically); (b) data are drawn or potential participants are identified from a record review of PHI; or (c) research generated data are entered into a participant's health record (Fisher, 2013).

Implications for research involving children.

Although a number of HIPAA standards are sensitive to the conduct of research involving protected health information, its focus on patients' rights does not easily generalize to social-behavioral, educational or medical studies that do not use or generate PHI. In particular, HIPAA's requirement that a legal guardian has the right to make

decisions for health care and to access the records of minors under their guardianship is potentially inconsistent with current Common Rule and Subpart D regulations permitting waiver of guardian permission for research participation (§§46.116, 46.408). If applied to all pediatric and developmental research, such a requirement could jeopardize the confidentiality of data protections to which child and adolescent research participants are entitled. For example, by late childhood and adolescence inappropriate disclosure of PHI to legal guardians may result in perceived privacy violations, feelings of embarrassment or humiliation, threats to one's medical or legal interests, and in some cases risk of parental punitive reactions (Cianciotto & Cahill, 2003; Thompson, 2000).

Application of the HIPAA rule regarding parent/guardian access to records is especially problematic in the initial phases of genetic research when there are no strong or reliable scientifically established links between a child's genetic makeup and current or future behavioral or medical problems. Guardian access to such information may deprive child participants of the "right not to know" currently afforded adults and their right to withhold information from others that may be detrimental to their self-interest (e.g., a change in parental behaviors based on an over or underestimation of the links between the genetic information and child development) (Fisher & McCarthy, 2013; Grandjean & Sorsa, 1996; Wilfond & Ross, 2009).

Recognizing that informational risk may change over time with advancing technologies, we agree with the ANPRM proposal that a standing committee be established to review and update current and new forms of information risk and risk protections as they emerge.

Categories of Data Security Protections

The ANPRM is considering additional uniform standardized data and information protection requirements calibrated to the level of identifiability of information collected. We believe such calibrations should be empirically informed by age relevant research to ensure adequate participant protections and guard against overly burdensome security protections for low probability and low magnitude information risks that could discourage the conduct of research critical to children's health and wellbeing.

Multilevel influences on information risk. We agree with ANPRM recommendations to provide guidelines on standard security protections based on identifiability, data collection medium, and data storage. However, we urge that the guidelines include examples indexed to age, population, and context and criteria for evaluating the equivalence of security protections not included in the finite list of exemplars. In addition, as pediatric and developmental scientists we are particularly aware of how informational risk to human subjects is differentially and multiply determined by: (a) the nature of the topic studied (e.g., mother-infant interactions compared to development of math skills or delinquent behaviors); (b) the medium in which it is collected and stored (e.g., web-based data electronically recorded and stored, biospecimens collected in research laboratories and stored in biobanks); (c) population characteristics (e.g., age, physical or mental health); and (d) research context (e.g., schools, hospitals, participant homes, public spaces). We thus urge caution in the ANPRM's use of the term "uniform specific standards" to guard against inflexible and de-contextualized data security criteria that could fail to identify information risk or set unnecessary restrictions on data collection, especially for pediatric and developmental research on socially sensitive issues.

Updating categories of identifiable information and standards for protection. Identifiable information is a dynamic category that changes with increasing knowledge and emerging technologies. For example, future technology may enable identification of individuals based on biospecimens or recordings of brain functioning. The ability to link data across social media and other websites and global positioning, phone and other systems is also growing exponentially. Recognizing that informational risk may change over time with advancing technologies, we agree with the ANPRM proposal that a standing committee be established to review and update current and new forms of information risk and risk protections as they emerge. We also believe it is critical that this standing committee include members with expertise in biomedi-

cal, social-behavioral and educational research with infants, children and adolescents as well as members with expertise on how these age groups utilize new and emerging technologies.

Information Disclosure

During the course of data collection child and adolescent participants may reveal information suggesting suicidal ideation, serious health-compromising behaviors, illegal activities, child abuse or neglect, or plans to harm others. Whether to keep such information confidential or disclose it to parents, professionals or legal authorities is a daunting ethical challenge for pediatric and developmental scientists conducting socially sensitive research (Duncan, Drew, Hodgson, & Sawyer, 2009; Fisher & Goodman, 2009; Fisher, 1994, 2003; Fisher & Fried, 2010; Lothen-Kline, Howard, Hamburger, Worrell, & Boekeloo, 2003; Thompson, 2000). Currently, neither the Common Rule nor Subpart D addresses this issue. We urge DHHS to explicitly state that investigators conducting child and adolescent research are permitted, but not required, to disclose confidential and identifiable information indicating participant self-harming, violent or illegal behaviors to parents, school counselors, health care providers or appropriate authorities when a problem has been discovered during the course of research that places the welfare of the participant or others in jeopardy.

Information Risk Oversight. We concur with the ANPRM observation that IRB members may not currently have the technical expertise increasingly required for data security, especially as NIH increases its efforts toward increasing data sharing, supporting national multisite longitudinal data sets, and biobanking of genetic and biologic data. We do not, however, support the recommendation to remove data security oversight from the purview of the IRB. The ANPRM is vague and ambiguous in its description of the oversight mechanisms that will ensure investigator knowledge of and adherence to data security protections and appears to place substantial weight on investigator education and self-monitoring. Given the complexity of both data security and data disclosure procedures in the absence of an effective and clear oversight alternative, we believe that IRB review provides the critical third-party oversight needed to ensure that investigators are aware of and implement best practices for data protection and participant welfare.

Improving Informed Consent

The Common Rule provides basic information about the required elements of informed consent, consent documentation and consent waivers involving all research with human subjects. The ANPRM contains an admirable list of suggested rule changes in response to criticisms regarding: the length, legibility and content relevance of consent forms; the time IRBs take editing and revising forms; ambiguity and inflexibility in IRB waivers for informed consent; and adequacy in addressing consent related to reuse or additional analysis of existing data and biospecimens. All of these proposed changes have particular relevance to child assent and parental permission procedures since Subpart D §46.408 refers investigators and IRBs to Common Rule §46.116 for information that must be considered when developing guardian permission and child assent procedures.

Length, Content and Documentation of Consent

We applaud ANPRM's efforts to shorten the length of consent forms. However, given the developmental, cultural, educational, and mental health diversity of research participants, we urge caution against requiring a standard form for the language content and length of consent forms. We also appreciate ANPRM's recommendations aimed at addressing IRB pressures to include informed consent components irrelevant to the specific research context and for which exclusion is permitted under §46.116c. These include burdensome IRB requirements for including statements about risks of low probability and for which there is no experiential or empirical support. For minimal risk research, too often in the absence of empirical or clinical evidence IRBs require investigators to include informed consent statements of "stress" or "discomfort" as a research risk when the probability and magnitude of such a risk is small or non-existent. Such statements can be deceptive and threaten scientific validity by unduly creating participant expectations of distress or harm. We recommend that when there is no evidence of specific risk, the default "risk" statement for minimal risk research should be: "*This research presents minimal risks no greater than those of daily life or routine medical, dental, psychological or educational examinations or tests.*"

Distinguishing participant risk from institutional liability. We agree with ANPRM recommendations to improve consent forms in ways that enhance prospective participant [and guardian] understanding of their

research rights and procedures. In particular we appreciate the ANRPM's willingness to address the problem of over-inclusion of institutional liability clauses in informed consent. In many instances statements regarding an institution's lack of legal liability refers to risks outside of the research procedures themselves (e.g., falling while walking down a hall) and thus do not belong in the informed consent. In addition, liability waivers included in an informed consent document clearly violate the regulatory language in §46.116, which states that no informed consent "may include any exculpatory language through which the subject or representative is made to waive or appear to waive any of the subject's legal rights or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence." This is particularly relevant to assent procedures for children and adolescents who may interpret such language as a prohibition against alerting adults to harms incurred during research participation. We strongly recommend that (a) institutional liability statements be removed from informed consent documents for research participation and (b) institutions that wish to notify prospective participants or their guardians about limits to the institution's legal liability do so in a separate document.

Oral consent and documentation. Informed consent is more than a document. It is a process that whether oral or written provides a prospective participant or their guardian with sufficient information to make an informed decision about participation and provides the opportunity and time to ask questions. The ANPRM has sought to clarify regulatory requirements and remove barriers to obtaining oral consent and documentation. Such consideration is particularly appropriate for pediatric and developmental research. For example, oral assent may be more respectful and less coercive for young children based on their more limited reading, deference to authority and lack of experience signing forms. IRBs should be encouraged to apply existing federal guidelines and approve oral consent and documentation procedures when: (a) a consent document is developmentally or culturally inappropriate; (b) a written document may jeopardize participant safety; or (c) research is conducted solely through telephone contact.

At the same time, in most cases older children and their guardians benefit from the availability of an informed consent information sheet that they can refer to as they consider whether to participate and during their participation (Cameron, Marsillio, Cushman, & Morris, 2011). Whether or not information is discussed orally with the prospective participant, whenever feasible we recommend providing participants and their guardians an information sheet (whether on paper or via the Internet) that includes the critical elements of informed consent. The procedure for obtaining oral or Internet assent or consent should always be documented.

Emancipated and Mature Minors

Under Subpart D §46.402 "Children are persons who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." This regulatory language refers to statutory definitions of "mature" and "emancipated minors" that permit adolescents to consent to healthcare without guardian permission. However, since most state laws do not include language specific to research participation many IRBs continue to treat emancipated and mature minors as children under Subpart D and needlessly require guardian permission or waiver of guardian permission for their involvement in clinical trials or research using surveys, interviews, or tests related to treatment and procedures for which they have obtained legal adult status. This deprives adolescents of their full rights and protections as "adult" participants under the Common Rule. For example, an adolescent who by state law has the right to consent to and obtain reproductive and sexual health medical care without parental permission should also have the right to autonomously consent to epidemiological, observational, interview and survey research exploring the antecedents and sequelae of adolescent sexual health behaviors and to intervention research on the effectiveness of related preventive and intervention strategies (IOM, 2004; Mustanski, 2011; Society for Adolescent Medicine, 2004). Failure of IRBs to appropriately apply the Common Rule rather than Subpart D to these and other adolescent stigmatized populations unjustly deprive them of research critical to their health and wellbeing.

We strongly urge OHRP to consider language in the Common Rule and in guidance clarifying that persons who by state law are considered "mature" and "emancipated" minors should be accorded adult status when they are asked to consent to participate in research on biomedical, social or behavioral factors related to medical services and procedures for which they are legally entitled to provide autonomous consent. For example, 15-year-olds living in states in which they have the legal right to seek sexual health services without parental permission should

be granted the same autonomy in deciding whether to participate in research on sexual health.

Waiver of Guardian Permission

Federal regulations for protection of human subjects include two provisions relevant to the waiver of guardian permission in pediatric and developmental research. Under Subpart D §46.408c IRBs can waive guardian permission if an investigator provides sufficient information indicating that it "is not a reasonable requirement to protect the subjects (for example, neglected or abused children)" and has proposed "an appropriate [substitute] mechanism" for protecting children during the consent process. Although unspecified in regulations, such protections often include the appointment of an independent participant advocate whose responsibility it is to ensure that each minor's participation decision is informed, rational and voluntary (Fisher, Hoagwood, Jensen, 1996). This regulation provides critical protections for minors when guardian permission is not in their best interest while at the same time providing opportunities for minors to participate in research important to the health and wellbeing of child and adolescent populations.

Under Subpart D §46.408b guardian permission can also be waived if research meets the requirements of Common Rule §46.116d: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect participants' rights and welfare; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the participants will be given additional information about the research. However, some IRBs find the broad language of §46.116d confusing in its application to child and adolescent research. Such language can lead to appropriate caution regarding the adequate protection of minors participating in research, or raise unnecessary barriers to the conduct of minimal risk pediatric and developmental research that offers sufficient child participant protections and that cannot be conducted without the waiver. Below we highlight two provisions of §46.116d waiver of guardian permission that we believe merit clarification in Common Rule changes or related OHRP guidance.

"The waiver or alteration will not adversely affect the rights and welfare of the subjects." Assessing adequate research protections for the rights and welfare of children and adolescents in the absence of guardian permission rests in part on their ability to provide informed, rational and voluntary consent. A significant body of empirical data on children's and adolescents' understanding of their research rights and research procedures has been generated and should provide the basis for assent procedures that are age-graded and fitted to the specific research context (IOM, 2004; Read et al., 2009). Additionally, there is a growing literature on methods to enhance children's understanding of research procedures and to encourage children and adolescents to assert their right to refuse or withdraw from participation (e.g., Bruzzese & Fisher, 2003; Eder, Yamakoski, Wittmann, & Kodish, 2007).

As Common Rule regulations are revised to provide greater specificity on requirements for informed consent we urge consideration of the relevance of §46.116(2) to research involving minors. We recommend that in contexts in which waiver of parental permission is appropriate investigators and IRBs be encouraged to: (1) draw on developmental research to ensure consent language is age-appropriate; (2) include educational procedures within the consent process that enhance minors' understanding of research and their research rights; (3) evaluate participant rights and protections within the context of existing empirical evidence on children's developing consent capacity; (4) when appropriate include standardized age-appropriate assessments of prospective participants' consent capacity; and (5) when the first four steps are insufficient consider the appointment of an independent participant advocate to ensure children's informed and voluntary participation (see Vitiello, 2008; Gibson, Stasiulis, Gutfreund, McDonald, & Dade, 2011; Masty & Fisher, 2008).

"The research could not practicably be carried out without the waiver or alteration." The term "practicably" in this regulation has caused considerable confusion in approval of consent waivers across research populations. Drawing on the Secretary's Advisory Committee for Human Research Protections (SACHRP, 2005) recommendations we offer the following suggestions for ethically applying this provision to waiver of guardian permission. We strongly support waivers of guardian permission for minimal risk pediatric and developmental research when the investigator has (a) developed adequate procedures for participant protection; (b) explored alternative methods of obtaining guardian permission; and (c) provided a reasonable argument that the scientific validity and scientific, educational and social value of the study would be compromised if guardian permission is required.

We also believe guardian permission should never be waived for investigator convenience or solely for reasons of cost or speed or other expedient measures if doing so

weakens protection of subjects' rights and welfare. Parents' reluctance to permit their children to participate in research is not a legitimate reason to waive this protection and is antithetical to the principles of beneficence, respect and justice. This happens all too frequently when investigators who find it difficult to obtain parental permission from historically marginalized populations request a waiver rather than consider the reasons for the reluctance and use such knowledge to increase sensitivity to and understanding of the research, recruitment and consent procedures within that population.

Informed Consent to Longitudinal Research, National Surveys, Data Sharing and Data Repositories

In recognition of rapidly changing data analytic and long-term data storage technologies, the ANRPM has proposed reforms for written consent for long-term use and secondary analysis of archival data in general and for biospecimens in particular. New security rules will have significant influence on data generated from longitudinal studies. Longitudinal studies allow for tests of continuity and change in developmental processes and the influence of genetic, social and environmental contexts over time and are essential for assessing the lifelong consequences of medical, educational, clinical, or other interventions. Whether archival data in longitudinal studies or national surveys are identifiable or de-identified, their contribution to society is greatly enhanced by secondary analysis.

Re-consent for use of biospecimens and socially sensitive data. Investigator access to pediatric biobanks and archives in which psychiatric, criminal or other socially sensitive information is stored raises questions of whether parental permission is sufficient to continue to use biological samples and other data after the **children** become adults (Fisher & McCarthy, 2013; Goldenberg, Hull, Botkin, & Wilfond, 2009; Twomey, 2010). We agree with the ANPRM's conclusion that there is no need for re-consent for future use of de-identified information, with one caveat. Future analysis of de-identified data by the original investigator or secondary analysis of de-identified data by other investigators typically poses no informational risk. However, emerging software and biomedical technologies may make original de-identification data security protections obsolete, and unknown at the time of the original consent. We therefore recommend that when children or their guardians provide permission for future use of data, the consent form indicates that all investigators who will have access to data in the future will be bound by the best practices in data and confidentiality protections at the time of data collection and new protections as they emerge. We recommend that this commitment is honored through ANPRM recommendations discussed earlier in this report to ensure and continually update the data security procedures that investigators and administrators of data archives and biobanks must follow to protect against information risk.

We also agree with ANPRM that identifiable information for which parental permission was obtained should be considered as default permission for continuation of use of data after the child has reached the age of majority as long as (a) appropriate security protections are in place and updated as may be required by evolving information technologies as well as federal standards and (b) the level of harm associated with informational risk has not increased with changes in societal attitudes, health coverage or other policies. However, as we move from the early stages of pediatric biospecimen research, further public engagement and empirical exploration of the attitudes toward re-consent of adults who participated in these studies as children is needed to determine how best to balance the potential scientific and social value of using these samples and respect for and sensitivity to participants consent expectations and concerns about privacy and trust (Goldenberg et al., 2009).

Linking archival data to the collection of new data. Protection of child and adolescent privacy rights require that when an investigator wishes to link archival identifiable data with collection of new data, re-consent must occur. We recommend that the consent should be for the new data collection and linking to the archival data set, *not* for the new investigator's initial access to the contact information of individuals who participated in the original study. Rather, access to participant contact information should be permitted to occur with a signed letter of agreement between institutions that security and confidentiality rules will be followed.

Conclusion

The ANPRM proposed changes to the Common Rule represent a watershed moment for the way scientists and IRBs will view their roles and responsibilities for the promotion of knowledge and the protection of human subjects for perhaps decades to come. Since the inception of the Common Rule, efforts to change federal regulations have rarely succeeded. This is not surprising given the moral, administrative and political complexities of constructing

regulations that meet the dual obligations of scientists, their institutions and their government to advance science and protect participant welfare. It is highly unlikely that a similar opportunity for regulatory changes specific to research involving children will be forthcoming in the near future. It is thus critical that the voice of pediatric and developmental scientists is included in public deliberations on regulatory changes to the Common Rule that will result from this historic juncture.

Historically, children have been denied the full benefits of scientific knowledge and evidence-based interventions essential to their health and wellbeing because they have been perceived as a population vulnerable to research harms. IRB reviews have often subjected research involving children to over-zealous protectionism (Hoagwood et al., 1996). The 1998 NIH mandate for the inclusion of children in research created a sea change in the interests of government and industry to fund pediatric and developmental research. This increase was not however matched by sufficient reassessment of whether existing ethical frameworks and regulations were appropriately calculated to the twin goals of access to and protection governing the responsible conduct of pediatric and developmental research (Kodish, 2005).

In writing this report, it is our intention to illuminate the linkages between the future conduct of pediatric and developmental science and proposed changes to the Common Rule. The stakes are high, and children have much to lose and much to gain. It is our hope that our recommendations assist regulators in adopting changes that will bring the goals of ethical and scientific pursuit in research involving children into closer alignment with the core ethical principles of beneficence, respect and justice. ■

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Commentary on

Preserving and Enhancing the Responsible Conduct of Research Involving Children and Youth

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The importance of considering children and youth in public policy cannot be over-stated, and Fisher et al. have rendered a particularly valuable service to the children and parents of the United States, as well as to researchers, IRBs, and, indeed, everyone else, by providing a clear, well-argued, and comprehensive review of the implications for the young of the proposed changes to the Common Rule. I agree with and endorse almost every point they make. In this commentary, I only touch on a few of their key suggestions and critique a few items in the ANPRM not mentioned in Fisher et al.

I heartily agree with the authors' endorsement of an age-indexed general population standard in the definition of minimal risk. The first time I heard a researcher propose a relative standard of minimal risk, the researcher claimed that members of the target population ran significant risks every day because of the violence endemic to their neighborhoods. This was used to justify research methods that would expose subjects to more severe risks than would normally be allowed in research on people in safer neighborhoods. I was appalled. To me, the very idea that it would be appropriate to increase the burden of the already underprivileged cannot be taken seriously.

Fisher et al. concur with the ANPRM's suggested changes to expedited review of research. I, too, concur with most of the changes, but the elimination of the annual review of expedited research makes me uneasy. When I present an overview of human subjects research, I often use the PHS Syphilis Study at Tuskegee as an example of a study that, given the racist practices and attitudes of 1932, might have **begun** under the regulations of the 1980s and beyond, but could hardly have **continued** for almost 30 years after World War II if a system of annual review had been in place.

I do not suggest that anything like the PHS Syphilis Study would be repeated today, but continuing review is important because times change – consider the advent of HIV/AIDS and the rapid development of technologies that are changing our understanding of privacy today. I hold that even expedited studies should include an estimated end date and undergo a final or closeout review. Studies that are projected to last more than 3 (5? 7?) years ought to be reviewed on a reasonable, but not necessarily annual, schedule. This need not be overly burdensome.

Fisher et al. "do not … support the recommendation to remove data security oversight from the purview of the IRB," and neither do I. The adoption of "standardized data protections" (ANPRM II.A) seems worth exploring, but, as Fisher et al. note, there must be "an effective and clear oversight alternative" to IRB oversight. The obvious alternative would be a new Information Security Review Board, but this would be an additional (and, I think, unwarranted) burden for institutions and researchers. Instead, it might be suitable to require IRBs to include a data security expert as a member. For IRBs that oversee research below some objective threshold of information risk this requirement would be waived.

Of the points made in the ANPRM not mentioned by Fisher et al., I will comment on three, presented from the least to the most important.

In section IV, the ANPRM suggests that the informed consent document should explain "why someone might want to choose not to enroll." How is the IRB to know this? Considering the careful attention the ANPRM pays to reasonable definitions of minimal risk, and the proclivity of IRBs to chase phantom risks, I am surprised that this statement is included. Surely a reasonable statement of benefits and risks

of the research, accompanied by a conversation with a sympathetic and well-prepared researcher, achieves the same goal without as much pre-emptive guess-work.

A more important flaw involves de-identified information. A laudable aspect of the proposed standards for data security states that "investigators would be strictly prohibited from attempting to re-identify the subjects of the information" (ANPRM V.B). Some of the value of this prohibition is undone in Table 1, "Proposal for the Excused Category of Research Involving Pre-Existing Information or Biospecimens," in Column 4, Row 4. This indicates that "registration of research with IRB" for "de-identified information" should not be required. The problem is that if the IRB is unaware that research is being undertaken with de-identified information, enforcing the ban on re-identifying data sets is rendered extremely difficult or impossible. Furthermore, such data sets could be passed from one researcher to another with impunity. The magnitude of potential harm this would carry, even if the probability of harm is low, is enough to warrant requiring researchers to take the minimal effort needed to register such studies.

Finally, I fear that the authors of the ANPRM have may have lost sight of the principle of justice in II.2.a.iii, which considers eliminating some of the current requirements for approving research that involve only minimal risk. Two of the criteria that are considered for elimination are that "selection of subjects is equitable" (ANPRM II.2.a.iii.3) and that "additional safeguards" are required for research with vulnerable populations "to protect the rights and welfare of these subjects" (ANPRM II.2.a.iii.8). There is a reason that the Belmont Report includes the principle of justice rather than letting the principle of beneficence do that work. Beneficence is primarily concerned with harm, while justice is concerned with rights. Risk, including minimal risk, is generally conceived in terms of harm, not the violation of rights. By removing these requirements, we increase the likelihood that members of vulnerable populations will be exposed to greater injustice, if not greater harm.

I reiterate my admiration of Fisher et al.'s report. Our current opportunity to improve the Common Rule must not be squandered. I applaud SPR and Fisher et al. for their contribution to this effort.

Commentary

Research with Young Children

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With the first proposed changes to the Common Rule in more than 20 years, research oversight is moving into the 21ST century, and it is critical at this historic moment that researchers' feedback on the proposed changes be considered. Much Institutional Review Board (IRB) oversight is tailored to biomedical research. At our university, even the nomenclature serves as a reminder of this focus. The IRB that reviews social-behavioral research is labeled with biomedical as the reference group, i.e., the "non-biomedical IRB." This is all fine and good; the risks associated with most biomedical research are generally greater, and studies of drugs, devices, and other biomedical interventions deserve customized scrutiny. However, what is relevant for review and oversight of social-behavioral research does not correspond precisely to that which is relevant for biomedical research. To the extent that biomedical research is the model, review and oversight for social-behavioral-educational research may not match the nature of methods and risks associated with such research. At our university in the past year, of the roughly 12,000 IRB submissions (e.g., initial, renewal, modification) reviewed by the IRB, approximately half were biomedical and half were social-behavioral. To the extent that the University of North Carolina at Chapel Hill is similar to other research institutions across the nation, it would seem particularly important to consider social-behavioral researchers' perspectives on the proposed changes.

At our institution last year, 28% of IRB submissions received involved children under age 18. When the Advance Notice of Proposed Rule Making was released, our university's Office of Human Research Ethics held a series of meetings to educate researchers about the proposed changes and to gather feedback that would inform the university's response to the changes. At one of the meetings we attended, it was noted that Subpart D, the section of rules governing research with children, was not changing. The implication was that researchers working with children would see few changes in general resulting from the proposed changes to the Common Rule, because Subpart D was not changing. As Fisher et al. aptly note, the Common Rule and Subpart D cannot be considered independently; rather, careful thought must be given to how the proposed changes would affect implementation of Subpart D and research involving infants, children and adolescents.

We strongly support Fisher et al.'s recommendations and hope that they will be used to shape the final regulations. Many of the proposed changes would have implications for research with adolescents, and Fisher et al. thoroughly explicate these issues. The research at our Child Development Institute focuses on children from birth to age 8. Below we highlight and expand on Fisher et al.'s recommendations regarding the informed consent process (parent permission and child assent, where appropriate) with younger children in mind.

We agree that efforts to shorten and clarify parent permission forms should not be achieved through requiring a standard format for content and length, particularly when there is an expectation that a single standard would work across biomedical and non-biomedical domains. We also support the notion that parent permission and assent processes should be developmentally and contextually appropriate. At our university, one assent document template exists for children aged 7 to 14. Within this wide age range, children possess vastly different reading abilities and conceptual understandings of risks and voluntariness as well as study content. We

would like to see the creative use of pictures and other technologies in the creation of assent documents that provide children and young teens the study information they need to know in ways that match their specific developmental level (Adcock, Hogan, Elci, & Mills, 2012; Dockett, Perry, & Kearney, in press). And researchers might consider asking children themselves to assist in developing research forms that are more understandable and appealing (Ford, Sankey, & Crisp, 2007). Regardless of the tools and techniques used, we support viewing assent developmentally; for younger children, assent is an acknowledgment of the research and an affirmation to participate, while for older adolescents, assent is equivalent to the informed consent process (Rossi, Reynolds, & Nelson, 2003).

We support Fisher et al.'s suggestion that oral assent may be more suitable for younger children. Asking young children with limited reading abilities to sign a form within their early elementary school settings, where they routinely defer to the authority of the adults around them, may be coercive. In addition, young children likely have limited experience signing forms, and may not understand the implications of putting their name to paper. We suspect that young children may view providing their signature as denoting the equivalent of entrance into a contractual agreement. In addition, some research suggests that children may feel that they should agree to participate in studies because parent permission has already been obtained, which compromises the voluntariness of participation by the children (Abramovitch, Freedman, Thoden, & Nikolich, 1991). On the other side of the coin, Abramovitch et al. also found that a large majority of 9- and 10-year-olds felt that they should be able to participate in a hypothetical study that interested them, even if their mothers did not like the study, thereby asserting their autonomy. As with many endeavors that involve more than one person, the specific methods employed in balancing the preferences, rights, and responsibilities of parent and progeny will need to vary across studies to remain responsive to varying levels of maturity and risk.

We would also like to see greater attention paid to very young children's verbal and nonverbal interactions and cues that might indicate their dissent—their desire not to participate—at various stages of the research process. We often conduct research in early education and care settings, in which young children participate in studies without their parents present. In such cases, researchers must be attentive to children's subtle verbal, nonverbal, or affective indicators signifying either an interest in continuing or a desire to end research activities (or at least take a break from them). Even if not explicitly required, IRB reviewers appreciate researchers taking the time to describe their proposed procedures for determining the willingness of the very youngest research participants to complete study activities when there is no direct benefit to the child from such participation. Even the youngest participants deserve for their voices to be heard regarding research participation.

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