October 17, 2011

The Honorable Kathleen Sebelius  
Secretary of Health and Human Services  
200 Independence Avenue, SW  
Washington, D.C. 20201

Dear Madam Secretary:

On behalf of the Children’s Hospital Boston, I would like to submit the following comments regarding the ANPRM issued on July 26, 2011. As an organization we are committed to the promotion of conduct of clinical research and have worked hard to develop a human research protection program that both permits important pediatric research to go forward while adhering to a robust human research protection program. We recognize that over time the clinical research environment changes and it is essential to evaluate regulations so that important and ethical research continues to move forward. Children’s supports all intentions to review our current regulatory environment to determine if and where changes should be made. We are pleased to offer comments at this time.

There are a few general concerns and themes that apply to many of the changes being proposed. We will discuss them separately. However it may be important to note these general themes as you review our comments.

1. The ANPRM concentrates on specific parts of the regulations without conducting a complete review of the entirety of regulations pertaining to research, or the relationship of the proposed changes with other sections, specifically subpart D (the extra protections for children). The process of revising the regulations should include reviewing and revising all sections and subparts of the regulations. In addition it is important to question whether specific changes in the regulations are required or whether a review and rewriting of guidance would accomplish the same results.

2. Although many of the changes proposed may reduce time and costs associated with IRB review, they do not eliminate many functions, but rather shift them to undefined and decentralized components within organizations. This has the potential to increase inefficiencies. In many situations responsibilities that are removed from an IRB will just be assumed by others within an organization.

3. There are several proposals that shift the burden of understanding and applying the regulations entirely to investigators. This is suggested in the utilization of a
registration process for “excused research” where investigators will need to assume responsibility for their own knowledge base and application of the regulations. It is also noted that removing the requirement for the IRB to review informational risks will now result in placing this responsibility on the investigator. Despite these shifts in responsibility, the regulations do not contain provisions for assigning, establishing and maintaining this responsibility by the investigator. A separate section of the common rule should be developed for investigator responsibilities, similar to the FDA regulations. In addition, if investigators are to be held accountable for their decisions, they must have required ongoing training in general investigator responsibilities that is beyond the scope of current training requirements, and would include detailed training on making the new determinations.

4. In several sections the proposal calls for discouraging specific reviews and mandating justification of specific actions taken by IRBs to OHRP. It is inappropriate to include this type of mandate in any regulation. Institutions have the right and obligation to implement any additional review mechanisms they deem appropriate and should not have to justify to regulatory agencies why they choose to do so. This type of reference in any regulation is inappropriate for any government agency and should not be included in any revised regulation.

As you will see from the comments below there are some changes that we can support at this time, others that we do not support and some which require extensive additional consideration and debate. Instead of responding to all the specific questions, we have decided to comment on the general topics proposed for revision and reference where they respond to specific questions.

1. **Proposed Changes to Exempt and Expedited Review**

In general Children’s asks that children not automatically be excluded in the categories when considering any revised and expedited review categories or processes. There are many situations including interviews and focus groups that would present no different risk for children than for the adult community and they should be considered equally.

**Excused Research**

Children’s supports the proposal to expand the categories of exempt research. However we do not support moving to “excused” categories with required registration, but no review, prior to initiation of the research. The reasons are listed as following:

- There is often wide room for interpretation in the categories for research. This has been evidenced by the many years or working with the current exempt and expedited review categories. Even with modifications and clarifications of guidance, there will always be room for interpretation. Investigators would be burdened with extensive requirements for appropriate training and education in
order to make these determinations correctly. In addition, investigators who do not make these determinations on a routine basis will likely find it difficult to understand the regulatory categories and interpretations. The proposal to allow investigators to register their research is likely to result in greater inconsistency of interpretations. The proposed registration process is similar to the current process of submitting a proposal to determine that research is exempt; therefore there is no time savings in the actual registration process for the PIs. IRBs do have the responsibility to make determinations of exemptions in a timely manner.

- It is unclear as to the expectations for an IRB to “audit” the registrations after the fact. If this is a category of research which is outside the jurisdiction of the IRB, it is inappropriate to ask IRBs to spend their time and resources performing such audits. If an IRB finds a registration that is incorrect, what will be the expectation of OHRP? Is this considered noncompliance that requires reporting? If so, there will be a large increase in reports being filed to OHRP for what is really no-risk or minimal-risk research. Will there be an expectation that the research needs to terminate until the appropriate review is conducted or would data not be allowed for publication? If so, it would seem that the risks of investigators needing to halt their research and then having it reported to regulatory agencies are greater than the requirement for an individual with appropriate knowledge and training prospectively agreeing that the research is indeed “exempt”/”excused” before starting.

We believe mandated auditing creates unnecessary regulatory burden on researchers, IRBs, and the regulators. It is not clear against what standards such audits would be conducted. Audit requirements would drive unnecessary documentation in research that is now exempt and may undermine the intent of the new rule. Institutions should have the flexibility to establish quality assurance/quality control mechanisms in a manner that is appropriate for each institution.

- We do not support the expansion as proposed for category 2. Survey research covers a wide variety of projects, the most challenging being research about illegal behaviors and sensitive topics (substance abuse, crime, risk taking behaviors for adolescents, STD, psychiatric disorders, error or competence and some genetic information). Creation of standardized data security protections only addresses informational risks. However, IRB review encompasses the review of other risks, such as recruitment strategies, reading and comprehension levels of surveys, institutional acceptability, incidental findings (subjects determined to be at immediate risk of suicide) and state laws. Categorically eliminating IRB review for any survey research would eliminate important human subject protection issues for some categories of research. If IRB review were eliminated, it is likely that institutions would still require some level of review for these categories of research. Rather than generating a new system, it may make more sense to streamline the process. There is already a fair amount of flexibility
in terms of designating surveys as exempt, however IRBs may not be aware or comfortable with using this flexibility. IRB guidance instead of revision would seem prudent.

- In general we support the expansion of the categories and recommend that a multidisciplinary group be charged to recommend additions to the list and to review and update them on an ongoing basis. We recommend the current process for determining exemptions for the following reasons:
  - Institutions, rather than researchers, are held responsible when research is improperly designated as exempt
  - IRBs (administrative staff) are better suited to understand the nuances of the regulations and to apply them consistently
  - Researchers have an inherent conflict of interest, and may not be able to objectively apply exempt categories
  - Researchers are likely to underestimate the risk of their proposed research

- Finally, the reference to “excused” or “exempt” should be changed to “research that does not require IRB review”. The terms exempt and excused are confusing and do not accurately reflect the nature of the research activities.

**Expeditied Research**

Children’s Hospital supports modifying the expedited review categories and reviewing them on an ongoing basis with the following comments:

- We support the proposal to not require continuing review on an annual basis for all protocols; however we do not support discontinuing complete elimination for specific categories. We strongly support allowing much greater flexibility in determining a period of time for review that may depend on risk and status of research activities, or even an extension of the time period (every 2-3 years), for minimal-risks studies or those open to analysis and collection of routinely obtained clinical data. Institutions maintain a responsibility for the oversight of ongoing research at all stages. If routine continuing review schedules are changed or eliminated, institutions will likely create new mechanisms to track such research. Rather than creating a new mechanism, the IRB infrastructure currently accomplishes this. We also support flexibility and the manner in which these reviews occur.

- There is concern in moving to a methodological list of procedures that are always determined to be minimal risk and eligible for expedited review. Methodological lists of procedures do not take into consideration contextual issues that may make a procedure greater than minimal risk for a group of subjects. The process to decide whether something is minimal risk is complex and often controversial.
This is evidenced by many federal advisory committees and IOM committees that were charged with making recommendations for interpretations of subpart D. During that process the advisory groups tried to agree on examples of procedures that could always be considered minimal risk. In some situations there was much debate about procedures, such as skin biopsies, glucose clamp studies etc. In the end, many specific procedures were not included as examples because one could not always say a specific procedure would always represent minimal risk. There were multiple examples in which a procedure would be minimal risk for a majority of subjects but could be greater risk in a specific situation. An exercise stress test is minimal risk for the majority of the population; however it is not minimal risk one day after a myocardial infarction. Therefore one could not conclude a stress test as always presenting minimal risk. This could prevent it from appearing on an expedited approval list as the ANPRM now proposes.

As an alternative approach we encourage the consideration of inclusion of a list as merely examples, allowing the IRB to determine the level of risk and thus whether a specific proposal would be eligible for expedited review. We encourage a model in which the responsibility for setting the terms for expedited review at each institution results in each IRB determining the level of review for minimal risk research as appropriate under local circumstances.

- The revised regulations make no attempt to clarify the definition of minimal risk. There is long-standing controversy as to whether minimal risk is relative to the daily life of the subject population or of normal, healthy individuals. Without such clarification, it would be difficult to develop an expanded list of minimal-risk activities that could be expedited.

- Children’s does not favor mandatory reporting by IRBs when they choose to override provisions for expedited review. There is nothing to be gained by adding such a reporting requirement to OHRP and it is not clear what the government would do with this information. Such a requirement increases the burden for institutions and IRBs and could foster an adversarial relationship between IRBs and investigators. One of the strengths of the current expedited review process is that it allows IRBs to determine the appropriate level of IRB review for non-exempt human subject research without fear of reprisal from the regulators. IRBs must continue to have this ability to objectively review research and determine the appropriate level of review.

- Children’s supports the development of an ongoing mechanism to continually review and revise any expedited list that is developed.

- We do not recommend a second set of criteria for review of expedited research. The current criteria do apply regardless of degree of risk. A separate set of criteria would develop a double-standard for research that requires prospective IRB review and approval, and would further complicate research studies that start
as expedited then move to full IRB review, and vice versa. The current regulations already provide sufficient flexibility through the inclusion of “when appropriate”.

2. Mandating One IRB for All Domestic Multi-Institutional Studies

Children’s Hospital recognizes the need to eliminate duplicative IRB review in situations where the protocol does not present any specific local, ethical or institutional challenges or differences. The proposal to mandate one IRB for all domestic studies is vague and lacks detail. There was no definition of multi-site studies. It was not certain whether the proposal was intended to focus on multi-center clinical trials or to include multi-site studies in the social and behavioral fields, nor whether it would apply to trials of 200 sites or 2 sites. There is concern that this may be a proposal that has moved too fast without giving due consideration to the several additional complex issues that need to be considered in requiring one IRB. The following issues are of concern:

- In 2009 OHRP requested comments regarding models of central review. To date no discussion of those results has been made public. Opposition to the use of central IRBs often exists because of concerns related to regulatory and legal liabilities. If a central IRB is used, allocation of regulatory liability needs to be addressed explicitly by OHRP and the FDA, as a means of clarifying roles and responsibilities, thus encouraging the voluntary use of central IRBs.

- The proposal assumes that all domestic sites are sufficiently similar so that a central IRB could assess the research appropriately for Common Rule purposes. Some domestic sites may have subject populations and risks attendant to the research that are radically different. While this may not be the case in all situations, a mandate for one IRB review fails to consider potential important differences which may exist and need to be considered at a local level. Children’s is specifically concerned about the expertise that is required for the review of pediatric research. The proposal does not address or emphasize the needs for expertise when a central IRB is assuming review responsibilities for multiple sites. This is of particular concern in the pediatric community.

In addition to widely different subject populations, such as pediatric research, other factors subject to significant variations among sites would include:

- State laws governing special categories of subjects and research data (e.g., genetic testing, genetic privacy, mental health information, mental retardation and developmental disabilities information, surrogate consent)
- Investigator conflicts of interest, requiring disclosure by investigators and analysis by local institutions relating to disclosures to subjects and other conflicts management strategies, which will vary from site to site, as potential conflicts vary from site to site
- "Emergency research" undertaken without subject consent, for which the FDA requires local community consultation
- Disparate cultural norms among populations targeted for recruitment
- Varying investigator and research team experience, which may require more or less local oversight during the conduct of the research

- Over the past 10 years institutions have worked hard to develop a human research protection program (HRPP) of which an IRB is one component. However IRBs and their administrative offices often serve a coordinating role for a well-functioning HRPP. IRBs receive information and feedback from other components of the HRPP and work simultaneously on different human research protections (radiation safety reviews, conflict of interest committees, pharmacy, nursing). The other components of the local HRPP interact with the local IRB so that these other issues are addressed. For some complex protocols, the separation of a local IRB from the remainder of the HRPP would have potential adverse consequences on human subject protections or at a minimum would delay the initiation of such work until all local issues are addressed. While this may not be an issue for all research protocols, a mandate to utilize one IRB eliminates an important human subject protective function when it may be necessary.

- Many issues that involve human subject protection arise after a protocol has begun. Compliance incidents, adverse events and unanticipated problems are usually recognized first at a local level. Many such events are related to a local HRPP program. For example a medication dosing error that occurs in a pharmacy or by nursing staff may represent systemic problems at that institution. Relying on an external central IRB to investigate, potentially request corrective action and possibly implement sanctions removes the ability or flexibility to address what is in most probability an important local issue. Local sites need to have complete oversight when things go wrong during the course of research. This cannot be delegated to others. Even if local sites are afforded the ability to conduct their own investigation, the central IRB has the ultimate responsibility for resolution and reporting which is not always appropriate.

- The use of central IRBs should be encouraged and the federal government should provide resources to develop central IRBs. However the decision to utilize a central IRB should be made by institutions on an individual research project basis. As an example, the NCI IRB has proved to be an effective mechanism by which a central IRB was developed and many institutions have opted to utilize it without a mandate. This is the pattern that needs to continue to be followed.

- There is no mention of the importance and relationship with accreditation. At the present time, accredited institutions may be more apt to rely on other accredited institutions. While AAHRPP accreditation is not a federal program or requirement (nor should it be), it is recognized by many of the top federally funded institutions in the United States as an essential gold bar to achieve. Sites who are accredited
should not be expected to potentially rely on a central IRB that may not be accredited and not meet the standards that they have achieved.

- There is no specification as to a mechanism by which the single central IRB could be selected, were this proposal to be adopted. Allowing an investigator or the research team to select the central IRB could risk exacerbating a process of “IRB shopping” to secure the most lenient or permissive IRB. A system could be developed by which sites could collectively agree on a central IRB. However this might lead to a default to IRBs of the largest, most influential institutions and over time, provide an increasing “market share” of central IRB business, and/or commercial central IRBs.

- If a central IRB were required, it could be limited to specific categories of research. If there were federally-developed and supported IRB models, such as the NCI model or the National Children’s Study, then perhaps federally-funded studies would use a central IRB review model. Otherwise the general concept of utilizing one IRB for a multi-center study would seem to make the most sense for the following situations:

  - Some multi-center industry sponsored FDA trials
  - Consortia that have developed a facilitated review process by which review occurs at the national level before the cooperative group distributes the protocol. The local IRB chairs can review all documents and decide to accept the central IRB review.
  - Multi-site studies for institutions that commonly work together. Such an arrangement has been achieved for all of the Harvard-affiliated hospitals where specific details and common methods of communication and recordkeeping have been developed.

- If a central IRB were utilized, there needs to be a mechanism so that all participating sites’ IRBs or ethics committees be given an opportunity to determine if there are any unique risks to their specific study populations, or any unique local ethical or regulatory issues that might arise in their conduct of the study. The local IRBs or ethic committees should be able to forward their comments to the central IRB for consideration.

- Costs of review and legal responsibilities for monitoring research and assuring its appropriate conduct would need to be appropriately allocated among a central IRB, local sites and their local IRBs, or other designated study reviewers. The cost of a required central IRB would need to be apportioned among the participating sites, or somehow accommodated in the overall research budget. It would be unreasonable to require one central IRB to review and monitor a study, but not adopt a corresponding mechanism by which costs for that central review and monitoring would be shared among the sites, or paid for by sponsors and funders, either directly or through indirect cost recovery. Any required local
review, however, would need to continue, with attendant residual local costs. A cost allocation, therefore, cannot be a categorical decision to fund a central IRB, but not any local review. There could be significant cost savings in a central IRB model for multi-site studies, but such a model would not eliminate the need for, and costs of, some measure of local review.

- There is no information on how the use of a central IRB would impact assurances or IRB authorization agreements and associated potential administrative burdens. Institutions that defer to one another in a central IRB process need inter-institutional agreements, by which central IRBs and institutions engaged in research can more specifically describe what each party would do in a functioning central IRB model. Without more specific OHRP guidance on these points, it would likely not be possible for the entire research community to establish inter-institutional agreement templates, while issuance of such specific guidance likely would ease and speed the emergence of templates.

- Were central IRBs to be used more frequently, as a result of this proposal or a voluntary increase in use within the research community, OHRP would likely need to increase its oversight of how these IRBs operate in the multi-site study context, and would need to be willing to impose sanctions, as appropriate, to assure that central IRB review is at least as effective in protecting subjects as local review. Also, consideration should be given to a process for qualifying a central IRB through accreditation or other means to assure that its takes into consideration local variations and issues, and appropriately communicates with the IRBs for which it assumed responsibility. At the current time, IRBs do not have the infrastructure and resources to develop these necessary arrangements.

In summary, we believe that at this time, a uniform mandate of central IRB review for all domestic multi-site studies would likely result in regulatory uncertainty and confusion. There would likely be failure of many central IRBs to review and consider local requirements and concerns, therefore resulting in a reduction in protection of human subjects. A more measured and careful process of encouraging central IRB use, accompanied in a step-wise and graduated manner way would be preferable. It is also essential that OHRP issue of guidance on critical issues implicated in the use of central IRB review. This gradual use of central IRBs would likely result in less disruption of the research enterprise, and eventually, an improved central IRB process based on experience. Such a drastic change cannot occur all at once since the infrastructure is just not there to support it. It also is worth noting that without a change in the Common Rule funders and industry sponsors currently have the ability to require use of central IRBs in multi-site studies and to implement this as a requirement at any time.

3. Informed Consent
In general, we believe that this section of the proposed regulations focuses too much on the consent form as opposed to the consent process, but we do recognize that some improvements to the overall process can be achieved through improvements to the consent form and related consent documentation. Children’s agrees that the informed consent process and form can and should be improved. Forms have become legalistic and complicated and are not an effective way for potential subjects to make an informed decision. The following comments are offered:

- Forms tend to be long and legalistic due to regulatory oversight. This includes legal and regulatory requirements as interpreted by sponsors, legal staff and federal agencies. In addition OHRP, the FDA and other agencies have at times made very detailed criticisms of consent forms for not meeting regulatory requirements regarding the elements of consent. This creates an incentive to make sure that each of the elements of a proper informed consent is addressed, regardless of whether it is applicable, and encourages IRBs to include study-specific regulatory citations in cases where they are not necessarily applicable. The regulatory incentives could be lessened if the agencies were careful to limit their citations. In addition federal agencies continue to increase requirements; such has been the evidence with GWAS data sharing, clinicaltrials.gov, HIPAA components and conflict of interest. The list continues to increase and it is important to note none of these requirements are required under the Common Rule.

- We do not agree that regulations should proscribe content or length. Consent forms need to become shorter in the majority of cases. IRBs should have the authority to determine the informed consent process and forms appropriate for the risk of the study. In addition regulations need to remain flexible to allow consent for minimal risk to be streamlined or perhaps modified to be more of a notification standard.

- Consents could be structured so that the ‘boilerplate’ and other items could be moved to the section of the regulations addressing the optional elements of consent (45 CFR 46.116(b). Only core, critical elements should be contained in the main body of the consent form. The rest of the information, including many required elements of consent, could be included in an addendum(s). The core elements that need to be in the main body of the consent include: (1) the statement that the project involves research; (2) the purpose; (3) the “voluntary statement” (including withdrawal); (4) the duration of participation; (5) the risks; (6) the benefits to public knowledge; and (7) the potential benefits to subjects. All other information could be codified in an addendum. Information included in the addendum could include, for example, the HIPAA authorization and the details for each study visit. It could also include the discussion of alternative treatments, compensation for injury, and information about GINA and clinicaltrials.gov, payments and tax ramifications etc.
The absence of a model or consent template makes commenting on this proposal difficult. The development of templates by OHRP could be very helpful; however this should be made available through best practices, not as a required mandate.

Consent in other cultural settings should be addressed for international research where community consent and other cultural requirements may be necessary. In these settings, it may be appropriate to have less emphasis on signed consent forms as the only valid form of documentation. Waiver of signature should be applicable to research, even above minimal risk, if culturally appropriate.

4. Consideration That All Specimens Are Identifiable and Require the Use of Written Informed Consent

Children's Hospital does not support the proposal to require that informed consent be obtained for all specimen use and questions the rationale that all specimens should be considered identifiable. The emphasis should be changed from considering whether specimens are identifiable to considering whether there is any meaningful risk if identification were to occur. The concerns are as follows.

- The requirement of consent could potentially limit the ability to perform important research with rarer conditions and diseases. Because only those samples where consent was obtained would be available for research, fewer samples would be available. This is of great concern in the pediatric research community because of the limited number of samples and potential rare disorders. The amount of research that has effectively been conducted with discarded specimens without harm to individuals does not suggest that we need major changes to the way we tread and handle specimens in research.

- There are many open-ended questions and concerns about how the requirement for informed consent would impact the use of pediatric samples when a child turns 18. While the actual proposed regulations do not address this issue specifically, there are concerns as to the expectations of the regulatory agencies. Currently, OHRP expects that if samples which were obtained from a child, continue to meet the definition of human subject research after that child turns the age of majority, one must obtain informed consent from the newly-adult subject, or the IRB must grant a waiver of informed consent. Another option would be to eliminate all identifiers or links and consider the use of the completely de-identified samples, "non-human subjects". The ANPRM proposes that all samples now be considered identifiable and no waivers be permitted. This means that unless the child can be located and consent obtained, samples collected with parental permission cannot continue to be used. This would apply to samples in both large and small pediatric tissue repositories. Although this is not specifically stated anywhere in the proposed revisions, the rationale and reasoning used to modify the current regulations clearly leads to this conclusion. This would
invariably result in the inability to use valuable pediatric research samples and have detrimental consequences for the pediatric research community. A potential solution would be to allow waivers of consent as included in the current regulatory guidance when children turn 18 and the regulatory criteria for waiver of consent can be met. This would need to be applied to biospecimens when children turn 18, even if not permitted elsewhere.

- The resources required to broadly implement written informed consent for participants, tracking those that decline and those that consent (plus potentially tracking check box responses), and tracking samples to designate those that existed prior to revised regulations from those acquired prospectively could become administrative and financial burdens which many institutions and the clinical investigation community may not be willing to support and sustain. This has the potential to eliminate future research use of clinical biospecimens unless institutions are willing to commit these resources.

- The proposal to use a brief general consent that allows for future use may be appropriate in many situations, but not ethically appropriate for all specimen uses as subjects may want more information (i.e. for creation of IPS lines or genome-wide sequencing). If the proposal to allow a short general consent is acted upon, it is likely that using short open-end consent for any specimen collection would become a standard of practice. In addition to contradicting the HIPAA regulations, the consent form may become less of a protection for subjects to understand how their samples may be used (i.e. for creation of IPS lines or for genome-wide sequencing).

- It is likely that in order to be able to obtain samples for research (especially those that were previously obtained under a waiver of consent), medical institutions would distribute forms upon admissions and visits. The ANPRM does not address the regulatory expectation for the informed consent process that would need to occur. Is there an expectation that there is a robust consent process in addition to a shortened open-ended consent form? In other words, is just handing a subject a form (i.e. at admissions or clinic visits) acceptable with no other contact? If there is an expectation of a detailed informed consent process, many institutions will not have the resources to devote to this, which may again lead to decreased availability of samples, or conversely, lack of appropriate human subject protections.

- There are many other practical issues that will require an inordinate amount of institutional resources. For example: what if subjects have questions, who will answer them; should patients be approached each time they come in; how will an individual know whether they previously consented; if you ask a subject each time, does that mean if they said yes once and then the next time say no, you do not allow any more tissue to be used? Although these issues can be addressed with complex computer infrastructure and staffing, it is not likely that may
institutions will have resources to allocate. The end result would again be the loss of samples for potential research use. Just as the proposed ANPRM wishes to limit the unnecessary expenses associated human research protections, this consideration should be of concern for resources and expenses at the institutional levels as well.

5. Strengthening Data Protection to Minimize Information Risks

Children's recognizes the importance of developing a strong data management plan for all human subject research but does not support the ANPRM proposal to adopt new data security standards patterned after the HIPAA Security Rule for all research involving identifiable data or limited data sets. In many non-medical research projects the use of a system that was developed to protect against the release of medical information to insurers, law enforcement and other providers does not make sense. The rule fails to provide any specific examples of breaches in the clinical research area that would warrant the adoption of these stricter standards. While we do not dispute that it is essential that there be data security standards for research data involving identifiable data, and that all institutions who engage in research need to develop, implement, monitor and educate staff to such standards, the proposal to adopt the strict HIPAA Security Rule standards as recommended cannot be supported. Children’s does not support adopting these mandatory data security standards and in particular, opposes using the HIPAA security and notification standards as a model. While some of these guidelines would be helpful in educating and informing researchers regarding data protections, they provide more protection than is necessary or appropriate. For example, it would be particularly burdensome to social behavioral investigators, as currently they usually do not operate in environments with HIPAA data security requirements. Any proposed rule changes must take into consideration the following issues:

- We recommend developing privacy and confidentiality protections specific to the research setting, rather than to apply HIPAA requirements that were never designed to apply to research. In addition, it is critical not to create new requirements for data security standards or extend the concept of personal health information (e.g. to biospecimens or DNA) so broadly that the burden of compliance effectively prohibits conduct of the research that has valuable benefits. Creation of HIPAA-like information technology infrastructure would be a major undertaking without a clear and recognizable potential for benefit.

- The HIPAA Security Rule provides extensive required standards which are intended to address security including administrative, physical and technical safeguards that require policies and procedures, training (e.g., encryption, access controls, etc.). While some of these guidelines can be useful in terms of educating the research community, the use of HIPPA-like provisions for all research data (such as data encryption, new breach notification standards, and prohibitions on re-identifying subjects) would provide more protection than is necessary or appropriate, especially in situations where there is little if any risk of
harm that could occur, even should a breach or incident transpire. In addition, application of HIPAA security standards could create significant and costly administrative burdens for institutions’ investigators and sponsors which must be justified and balanced with the risk that the requirement is intended to address.

- Applying the HIPAA standard could expand the scope of what is personally identifiable and, consequently, would expand the scope of what is considered human subjects research under the Common Rule. The effect would be to increase the circumstances under which informed consent and IRB approval are required, which again could unintentionally increase the burden on IRBs and researchers and in our opinion is contrary to the intent of the ANPRM

- There is no mention in the proposed rule as to which part of the agency would be responsible for implementation and oversight of such data security standards. We believe this is an important consideration which impedes being able to fully comment on the proposal.

- HIPAA is a highly structured regulation with little nuance allowed, to the extent it imposes a predetermined, all-or-nothing paradigm on (a) identifiability and (b) risk assessment. That is, there is little flexibility for IRBs to calibrate review based on likelihood or magnitude of harms. Accordingly, there has been criticism for several years that the rigidity of these standards does not translate well into the clinical research context where it currently applies.

6. **Establishment of an Improved, More Systematic Approach for the Collection and Analysis of Data on Unanticipated Problems and Adverse Events**

We do not believe that collecting all data on adverse events and unanticipated problems collected in a central database would increase human subject protections significantly, because we do not think that a central agency could interpret the data in any meaningful way. Individual patient information is anecdotal unless evaluated within an appropriate context.

- Evaluating an adverse report to determine if it has implications for others is something that takes significant time and often requires specific expertise for evaluation. Just collecting the events centrally will not add to any research protections unless the evaluations will be performed. Patterns need to be established before this information becomes data that is useful for consideration. Given that each trial is different, trying to establish these patterns in a large data set from diverse studies will be difficult if even possible. This will therefore take a lot of time and resources to be useful. We are not sure how just entering this data in one location will improve human subject protections.
• Many of the reasons causing current confusion and inconsistency in adverse event reporting have more to do with the requirements, definitions and interpretations of the agencies than the lack of a PI or IRB reporting the events. Before moving to a large database that may be very complex the regulatory agencies should harmonize and develop consistency in common terminology and definitions otherwise the use of one database will be meaningless. For example device and drug regulations use different standards and definitions of unanticipated risks and required reporting. The cost of maintaining this single large repository would be significant. The work involved should be reviewed prior to making any decision on this type of database that may be redundant and already exist.

• It is not obvious that this type of data collection would be useful to assess the effectiveness of the human subject protection system. While the data collection could provide basic information about the number of subjects and the relative risk, it is not clear that it would provide any meaningful information about the effectiveness of the system.

Children’s supports harmonization of definitions, interpretation standards, and reporting timelines across agencies to the extent that unique agency needs continue to be met.

7. Extension of Federal Regulations

Children’s supports closing the gaps of coverage for human research protections, however it is noted the current proposal will not accomplish this. Voluntary application of the Common Rule regulations occurs in many settings, however current gaps in coverage are not desirable. A solution is needed to extend appropriate protections to all research subjects without arbitrary limitations or gaps in coverage. The rule-making will extend to some gaps, but will not affect those that fall outside of institutions that do not receive any federal funding. The concerns with the proposed ANPRM are as follows:

• The proposal will increase regulatory burden for institutions by expanding the scope of prompt reporting required for research that is not subject to the Common Rule for unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspensions or terminations of IRB approvals. It is not clear that this additional reporting alone increases human subject protections.

• It makes little sense to ask that the common rule be extended without consideration of the subparts also being extended, as these are the protections for the most vulnerable of subjects. Even the different governmental agencies currently do not adopt the subparts which can lead one to question the desire to extend the regulations outside of federally-funded research. The intention to have one set of regulations that applies to all citizens should be a goal. However,
implementing it with such large gaps and inconsistencies continues to foster a “patchwork approach” which contributes to inconsistencies and lack of harmonization resulting in issues of noncompliance.

- A partial solution (e.g., limited to institutions that receive federal funding, as currently proposed) could lead to unintended consequences. While gaps currently exist, ambiguity does not exist in what is covered, namely research with federal funding is subject to the Common Rule and research with investigational drugs and devices is subject to the FDA regulations. A partial solution would create ambiguity where it does not currently exist. It could foster an environment where investigators and sponsors seek out institutions that receive no federal funding (and were thus exempt from Common Rule) and avoid those that do receive federal funding. There is also a potential consequence that institutions would now have motivation to avoid receipt of federal funds, in order to make themselves more attractive to investigators and sponsors as a risk-management strategy.

- There are also a host of practical questions related to implementation. For example, if a smaller institution receives a single federal grant, thereby triggering extension of the Common Rule, does that obligation remain in perpetuity, or does it revoke with the end of funding? What about funding from federal agencies that have not themselves adopted the Common Rule? There may be questions about the federal authority to extend coverage in the manner proposed, raising the potential for legal challenges to the extension through rule-making.

In conclusion we support a goal of closing the current gaps in coverage. However a more comprehensive solution would be congressional legislation to bring all human subjects research under a single set of regulations, including subparts, enforced by a single regulatory agency.

8. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

Any changes undertaken as a result of any final rule issued in accordance per the ANPRM must be harmonized across OHRP, FDA, OCR, NIH and all agencies that are involved with the support or oversight of research. It is not clear how the proposed changes will impact FDA regulations at 21 CFR Parts 50 and 56. Unless FDA endorses the same changes we will be left with a confusing and conflicting regulatory environment. There is a current need to harmonize to the greatest extent possible inconsistencies in interpretation and implementation across Common Rule agencies. It would also be helpful going forward to issue joint guidance by OHRP and FDA.

We appreciated the agency’s decision to extend the comment period. This provided an important opportunity to provide a more complete and detailed response. We realize that the purpose of the ANPRM is to stimulate discussion and obtain early important input.
from the stakeholders of the clinical research community regarding improvements in the IRB review process. While the proposal offered many new ideas and concepts, many were vague without detail. As we all know in the IRB world “the devil is in the details”. Lack of details in some areas made it very difficult to offer more informed responses; instead we could only offer broad and conceptual comments. We hope that before preparing any additional NPRM, OHRP reviews the submitted comments and continues to seek advice from experts in the IRB, regulatory, investigator, sponsor and subject community as a way of developing and providing a more detailed NPRM. While many proposals seem inviting at first, once the details and future implications are considered, they may raise more issues than they are trying to resolve. Thank you for considering the comments submitted from Children’s Hospital Boston.

Sincerely;

[Signature]

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