The American Society of Human Genetics
Policy Statement

October 11, 2011

ASHG Draft Comments in Response to Common Rule RFI

Introduction

The American Society of Human Genetics (ASHG) welcomes the opportunity to provide comments in response to the Request for Information on the Advanced Notice of Proposed Rule Making for "Human Subjects Research Protection: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators". Our comments reflect the consensus of the leadership of the world's largest human genetics professional organization. ASHG comprises more than 7000 researchers, clinical professionals, trainees, and advocates in the many areas of human genetics research and care. ASHG strongly endorses the principles of protection of human subjects and respect for the individual, in a context where the proposed modifications under review reflect the degree of risk in research involving humans. We think that adjustments to the process of review, approval, and follow-up for studies are essential to facilitate research and improve access of individuals to studies that could provide deep insights into mechanisms of disease and potential for significant intervention. We believe that this first ANPRM provides important steps in the improvement of the human subjects review process.

This document addresses five major areas of special interest to our research community:

1. Reduction of regulatory and procedural burden;
2. Multicenter research projects;
3. Simplification of the consent process and forms;
4. Clarification of regulation of use of biospecimens; and
5. Establishment of uniform regulations among all Federal agencies.

In each section, the specific questions from the ANPRM that are, at least in part, addressed will be listed at the end of the section in [Question #]. This specificity may help in referencing specific topics, while permitting our comments to be in a coherent and responsive document. This document is written in general terms at this stage in the rule-making process. Many specific and more nuanced responses will be made as detailed changes to the language of the Common Rule are proposed.

Reduction of overall burden of regulatory processes and procedures

We are concerned that the current process of review and approval is onerous and limiting the inclusion of some researchers, research sites, and subjects who view participation in research as the key to the improvement of people with their disorders. The shared goal in our communities of researchers, clinicians and families is to enhance the engagement of subjects in research, while assuring that subjects understand the research and that their inclusion in the study is voluntary. Extended time for review with multiple iterations of even insignificant changes in language currently characterize some IRB processes causing increased workload and costs for investigators and reviewers. These delays have resulted in the exclusion of some institutions from multi-site studies, and have excluded some eager subjects from participating in research.

We think that calibration of the review process to the risk of research to the subject is vital and achievable. Simplification of the documentation required and a streamlined review process are critical for observational studies, surveys, focus groups, or other activities in which the reasons for the data collection are explained and the subject voluntarily participates. This class of study usually should be administratively designated as "without risk" or "posing negligible risk" rather than "non-human subject research", and then the research permitted to proceed without IRB review. This change would align the OHRP and Common Rule language with respect to the degree of risk and be clearer to investigators and subjects. [Question 12]

The genetics community has many instances in which survey data are essential to the analysis and interpretation of results. We think that "without risk" may not be the appropriate designation for surveys with certain very personal questions that subjects may wish not to be revealed in a form that links the responses to subject. However, we believe that family history questions in the context of nearly all research pose negligible risk to the subject or family members for whom the subject has information [Question 6] The HIPAA definitions and protections of information have provided confidentiality in the context of clinical care and it is reasonable to expect that the same protections would apply to this type of information gathered for research with the HIPAA security measures in place. [Questions: 40]

The application of the definitions of HIPAA regarding health care operations and research will be very useful, as determination of quality improvement studies and public health program assessment, for example, should not be burdened with the research IRB protocols. Again, it is the protection of the information gathered that assures privacy, rather than review of data collection or analysis of protocols posing negligible or no risk to those from whom data are gathered. [Question 25] Encryption algorithms may also be useful in protecting the subject information, but may not be necessary. [Question 62] The Common Rule should be changed to address quality improvement, public health and program evaluation studies as health care operations as distinct from research activities. [Question 25]

Multi-center projects and trials

The proposed requirement of one central IRB of record for multi-center investigations is an important element in the ANPRM, and is applauded by the genetics research community. The current requirement for the IRB at every site to review the proposal and agree on language has delayed the start of studies, caused withdrawal of some investigators from studies, and robbed the potential participants at that site of the opportunity to be in an important study. At least two factors have contributed to these difficulties. The first is that the approval to include aspects of the proposed research may differ among institutions. Second, the wording of consent required by each institution may differ and, as a result, the nature of the work and some characteristics of the subjects who agree to participate may differ. Finally, the burden of reconciliation has fallen to disparate investigators faced with IRBs that have not communicated among themselves or reached a consensus on what can be approved and how to approve it. [Question 34]

The language of the policy adopted must be clear and the definitions precise. We urge the requirement of the designation of a single IRB for multi-center studies. [Question 31] Selecting

the IRB at the home institution of the PI would be optimal, but if more experience is available at the institution of a co-investigator then that IRB could be designated with the consensus of the investigators. Once the review is completed in a timely manner by the designated institution, the responsible (central or of record) IRB would circulate the approved materials to the other IRBs, and deal directly with any concerns raised. This process would necessarily be time-limited, assuring both communications among the IRBs and time efficiencies for the investigators. [Questions 32, 35] The concept of centralizing the consent process at one institution for a multi-site trial will facilitate research and assure that all potential subjects at each initially identified institution have the opportunity to be engaged in research. Agreement among IRBs should be facilitated by the standardization of individual consent forms as proposed in the ANPRM and discussed in the next section [Question 38].

Consent forms

Our researchers agree that consent forms have become too long, complicated and legalistic, such that the explanation of the research may be dwarfed by other language. The purpose of informed consent is to assure that the subject understands that the request being made (for samples, activities or information) is research, that participation is voluntary, and participation is not required for the provision of usual care. The nature of the consent forms, like the complexity of IRB review, should be attuned to the risk involved for the subject. In genetic studies where the specimens or data (even de-identified) will be put into large repositories, the consent must include this explanation. A simple but affirmative "opt-out" process for storage and reuse of left over specimens may be sufficient in many cases. [Question 50] Had this option been provided in the newborn screening process, we might have maintained an intact national system of residual bloodspots.

The issues involved in linkage studies to search for disease loci may be more complex and include challenges such as identification of disparity between reported and established paternity. Exome or whole genome sequencing studies could identify unexpected variants related to deleterious consequences. Finally, interventional studies such as stem cell transplantation, use of direct viral or other vectors for gene therapy raise the same issues as implantable devices. It is clear to us that the perceived risks in each situation differ and the consent form should reflect the specific issues and reciprocal expectations of the investigator and subjects. [Question 51]

As a scientific community, we look forward to the implementation of simple, straightforward model of informed consent formats that can be adapted across many types of studies. We think these models will eliminate the variation of interpretation of rules by investigators and their local IRB's. These models should make the process smoother and more collegial, and focus on the appropriate persons-the subjects. [Question 53]

In the instance of involvement in large scale genome sequence studies or analysis of variants, we think that the current focus on the hypothetical likelihood of "identifiability" is misplaced [Question 58]. Instead, we suggest the emphasis be placed on the choice by subjects to allow samples and/or information to be gathered into data or bio repositories, with the assurance that the data content will be available only to those with appropriately confirmed reasons to have access, and that the information is secure under the same protections as any medical record (i.e.,

HIPAA). The genetics community has been dealing with such sharing or critical information in databases and access to research-approved samples for some time, without serious breach of personal autonomy. Details of the process will need to be put in place, but the experience of specific groups can be utilized to streamline and improve these procedures.

Our interdisciplinary community will continue to discuss the implications of re-identification as genetic science expands and genetic data are incorporated into medical records, and we look forward to addressing issues around this topic more specifically as the ANPRM process moves forward.

In the future, new broad and simple consents should be instituted as a rule, with re-consent necessary in some well-defined circumstances. The genetics community also recognizes that "context matters" and that there will be rare exceptions to either the current or future "usual and ordinary" process. Such circumstances as the study of especially vulnerable groups or populations may need more investment in subject protection, but this should be a collaborative effort among the population, investigators, and the IRB process. [53, 54]

Issues regarding Biospecimens

We recognize that any individual from whom a biospecimen was obtained could be identified, with adequate information from current biomedical and bioinformatics databases and a second sample from that individual. Under most circumstances the harm to the individual from whom a sample was obtained, if identified, is likely to be small or none. We are, nonetheless, concerned to maintain our respect for the persons and groups or populations involved in research projects Therefore, we propose that in the course of establishment of biorepositories or others types of aggregates of data derived from individual the following principles be followed, and the processes embrace the following:

1. The subject is provided a clear opportunity to accept or decline the offer to participate in research that could result in submission of detailed information to an accessible database;

2. The information collected is protected by defined standards, such as the HIPAA requirements now a part of the US clinical landscape; and

3. The information or samples are protected against unwarranted access by standard procedures (certificates of confidentiality or privacy, defined access to data) that still permit information to be shared with defined investigators, while at the same time protecting against the inappropriate identification of individuals in the database or biorepository.

We believe that the more specific improvement and routine application of processes that have been developed in the establishment of huge databases and repositories for genetics, could serve the public and the research community well. The collection of enormous amounts of data in core facilities can speed research and improve data interpretation greatly, while subjects remain protected as promised at the outset of the study. [Questions 57, 58]

Uniform standards across agencies

The various US federal agencies that support research that involves human subjects have different missions and responsibilities and began their involvement at different times with different prevailing notions of the rules of engagement. The consequence is that rules differ among agencies, even to the extent that joint funding for research may involve incompatible requirements and limit the ability to complete the funded work. While it is a daunting venture, we believe that the rules by which research that involves human subjects is approved and regulated should be the same for all agencies (including the NIH, FDA, and DOD, as examples). We recognize that this will be a difficult process, but the proposed objectives of simplification of review and consent presents the best opportunity to act. We think that a standard vocabulary and definition of shared principles will be a first step. For example, the proposal to use HIPAA standards to protect research information may be awkward at first, especially when currently non-covered entities become involved. Nonetheless, the standards are well-defined, clear, used by clinicians in their work, and are translatable to the research setting.

The United States policies, including the Common Rule, have driven the development of processes to regulate research involving human subjects in many jurisdictions, although the restrictions in the Common Rule go further than many countries deem necessary. As the US medical care system and its data are neither fully integrated nor longitudinal as in many countries, some of the special restrictions on data and specimens derived from the US may continue to be necessary. However, as most research can be expanded to other jurisdictions (at least in genetics), it is important that the newly developed guidelines and processes allow recognition of research initiated in other countries. Any clarifications that can be made in the complex US system would serve to facilitate international research. [Questions 73, 74, 75]

Conclusion

The American Society of Human Genetics agrees with the principles put forward in the ANPRM. We have provided initial comments from the Board of Directors that reflect the special perspective of the genetics community and we have made proposals that we think will universally assist the process of research involving human subjects. This ANPRM represents the first step in a process and the American Society of Human Genetics wants to make it clear that we are invested and fully engaged in this process. We welcome any response to our comments, and we expect to contribute to contribute in meaningful ways as this process moves forward.