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The Honorable Sylvia M. Burwell  
Secretary of Health and Human Services  
U.S. Department of Health & Human Services  
200 Independence Avenue, S.W.  
Washington, D.C. 20201

January 22, 2015

Docket no: HHS-OPHS-2014-0005

Dear Secretary Burwell:

We, the undersigned, who represent millions of patients and their families, researchers and clinicians, offer these comments on the Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care. As currently written, the guidance is likely to cause substantial harm to both current and future patients by creating administrative barriers to receiving their care in the context of research, while leaving them exposed to identical or greater treatment risks without being informed about those risks, and without generating any knowledge to guide the care of future patients.

This guidance will impact research that is critically important to all Americans and most specifically to the millions of individuals we represent and/or care for: those who suffer from conditions and diseases that burden them greatly. We believe the draft guidance, intended to protect human subjects, will instead delay the development of critical information that can improve health, while affording minimal benefit to clinical trial participants. We are so concerned by the guidance that we have chosen to articulate our concerns in a single letter rather than mount a letter writing campaign, in the hopes that a single letter, from multiple stakeholders, raises the issues that are of a concern to participants/patients, academic and industry researchers, advocacy organizations, and clinicians.

The guidance claims that differences in endpoints that are the purpose of research are reasonably foreseeable risks. We are concerned that as a result, research that randomizes between two common treatments where there is no known difference in risk will have to (falsely) claim that there are substantial risks to being a research participant. This means that large pragmatic trials that compare usual practice, e.g., what commonly prescribed doses of aspirin are more effective at reducing risk of heart attack and stroke, will have to include as risks of the research, increased risk of death, heart failure and stroke. This also means that such trials will not be seen as minimal

risk by IRBs given that a potential increased risk of death can not be considered minimal risk. As a result, IRBs and researchers will be unable to make use of regulatory options that currently exist (such as waiver of documentation of consent or waiver or alteration of consent) that requires a finding of minimal risk. This will make many valuable trials, which could save tens of thousands of lives, impractical to carry out. Of note, research presented at a recent Institute of Medicine Workshop found the vast majority of the public surveyed (<https://rompethics.iths.org> [\(link is external\)](#)) stated that they do want to be told about comparative effectiveness research (by their physicians). However, if documentation or consent itself makes it too difficult to carry out research, they would prefer to relax consent requirements to ensure that this type of research can be conducted. Thus, the guidance will jeopardize many valuable trials, in direct contradiction to the views expressed by the majority of the public and of the membership of our organizations. The guidance will have great cost in lives lost and impaired quality of life from the resulting lack of knowledge about the best treatments.

Specific concerns follow:

**Assessing interventions doesn't necessarily represent risk.** IRBs should have guidance to help them assess whether the difference in known risks and benefits of two usual interventions are so sufficiently documented or proven that the research itself is unethical and efforts should be directed at a national effort to revise the usual practice. When there is no consensus in the relevant field that one intervention or array of accepted options is preferable over another, the likely variation in outcomes is the fundamental purpose of the study, not a risk of research participation. This should also apply to variations in interventions applied without empirical knowledge that one is superior. The lack of known theoretical and empirical differences in risks between two commonly used interventions should not automatically mean that an external decision (by a research study) to assign one or the other automatically elevates risk. At the same time, we are NOT recommending conflating lack of information about differences in outcomes with a license to randomize to different regimens about which participants would plausibly have strong preferences (e.g., surgery vs watchful waiting for prostate cancer).

**Uncertainty does not equal risk.** Uncertainty by itself does not pose substantial direct research-related benefits or risks beyond those associated with usual care. Presenting a guidance with a focus on risks downplays the importance of research, chills participation and is not balanced. Further, we are concerned that the risks associated with all known usual practice interventions will be conflated with the risks of participating in the research itself. Both the IRB and potential research subjects should evaluate the risks that may be inherent to the condition or disease state and to the standard treatment separately from the risks of participating in research. Otherwise, it will become very difficult to effectively evaluate usual practices, many of which are based on low quality evidence.

**Randomization itself is not automatically a risk.** Randomization itself should not be automatically considered a risk to research participants. Language such as the following leads to conclusions that randomization always poses greater risk for patients: "When a research study assigns the specific version of the accepted standards of care to be used, it is almost certain that at least some of the subjects will receive a different standard of care than

they would have received if not participating in the research. Indeed, in the common study design where subjects are randomized equally between two treatments, approximately half of the subjects will be assigned to a treatment different from what they would have otherwise received.” Different treatment does not necessarily mean greater risk. The regulations vest IRBs with the responsibility for determining when research involving randomization introduces risks that are *beyond or greater* than what a patient would otherwise experience. Mere difference in treatment or intervention should not automatically trigger a conclusion that greater risk exists. This point resonates particularly in those cases where lack of knowledge of any meaningful differences in risk or efficacy between interventions results in clinical care decisions being routinely made in a way that is arbitrary, since there is by definition inadequate knowledge about which is better (somewhat analogous, but not identical to random assignment). This is also the case when there are small differences in the relative risks between two interventions.

**Risk common to usual practice.** The guidance should recognize that when an identified risk is common to one or more usual practices, it is not reasonable to consider that risk as a risk that may result from the research itself.

**Recommendation regarding process for determining ‘risk’.** OHRP should provide additional guidance on the *process* that should be used to determine which risks are “risks of the research” *and* if a risk is foreseeable and therefore should be disclosed to research subjects. This additional guidance should take into account the points noted above.

**Participants active in the process.** The guidance should recommend robust engagement of participants and/or patients. It should not shield them. The traditional model of “Consent” is overburdened in the research context, and is generally not a useful process to the participant. Consent should return to a relational, and not transactional, engagement. We must ensure that participants are part of the process, since they are quite capable of understanding within the context of their lives. People understand what is at stake. Decisions should be based on availability of credible evidence, including the frequency, severity and context of the risks. The guidance should explicitly mention that this discussion of participant involvement and decision-making in risks of research does not apply to minimal risk interventions where the IRB has determined that a waiver of consent is appropriate.

**Participants need more than just *risk* information.** The OHRP guidance should be clear that the information participants need to decide whether to participate in a research study goes beyond *risk of harms*. IRBs should not take the guidance as license or encouragement to expand greatly the risk section of their consent forms. The guidance must make the point that not everything measurable is a risk. The guidance needs to define ‘foreseeable’ risk more narrowly. The guidance should recognize that risks of harms can be minimal, but there are other reasons to communicate information about study goals, study rationale, etc.

**Consent should be a relational activity not a regulatory formality.** The guidance should promote a culture shift, in which individuals are not subjects, but are participants, albeit with rigorous standards for evidence upheld and continually improved upon. Participants need to

be engaged in a trust context that no longer needs to be either expensive or complicated, since various networks, and the technologies used to connect them are deployable in health and research settings. The guidance should be attuned to the new, networked digital age, calling for solutions that make full use of current engagement, communication, and recruitment methods.

**Contextual approaches to consent.** The guidance should reflect that usual clinical practices are contextual, as is the consent process, and may differ based on the individual’s race, ethnicity, sexual preference, geographic location, values, community and various perceptions.

**Do not undermine IRBs.** It is critical that guidance is provided, and that IRBs’ ability to determine the level of risk that needs disclosure be aided, rather than impeded. OHRP should use clearer language, without rigid requirements for IRBs. Rather, it is important to recognize one-size does not fit all, and IRBs need to be confident that there will be no “gotcha” after the research is completed if the review process is performed in good faith. The current language is likely to create unnecessary unease and anxiety on the part of IRBs, and cause increased delays as IRBs struggle to discern the appropriate action. This dynamic can deny future patients the benefits from the evidence gained from research to improve their care. We recommend avoiding post-hoc finding of fault after a good faith process conducted by a registered IRB.

**Develop evidence about patients’ and subjects’ preferences.** The guidance should support a learning healthcare system, and recommend that stakeholders (including research participants) undertake empirical research to obtain data on how patients and subjects interpret risks, benefits, and information, moving us to think about “evidence-based guidance.”

**Cluster randomized trials.** Cluster randomized trials are a very important component of comparative effectiveness research, and a critical tool for evaluating intervention efficacy, particularly delivery systems interventions. IRBs should be given guidance for the evaluation of cluster randomized trials that preserves the ability to randomize at the provider or facility level for appropriate types of studies, which will allow the rigor of these designs to be maintained while providing appropriate protections for research participants, including the possibility of waiver of consent for minimal risk interventions. It is particularly important to permit cluster randomization to evaluate management strategies that are currently implemented as a matter of policy. Examples include care management plans, staffing levels, and formulary decisions. Furthermore, topics that are suitable for cluster randomization with notification, but without individual informed consent, should serve as a reference frame for IRBs when considering the information that should be disclosed during individually randomized trials of similar topics.

This nation needs OHRP’s leadership to facilitate research critical to individuals, families and communities while protecting participants. We believe modification of the guidance can accelerate discoveries that lead to better health for all.

Thank you for your consideration of our comments. If any of our organizations may be of further assistance, please contact [Tetyana Murza](#).

Thank you very much.

Respectfully,



Sharon Terry  
President & CEO, Genetic Alliance

**Organizations:**

AliveAndKickn  
Haworth, New Jersey

Alpha-1 Foundation  
Coral Gables, Florida

Alstrom Syndrome International  
Mount Desert, Maine

American Association for Respiratory Care  
Irving, Texas

American Behcet's Disease Association  
Rochester, Michigan

Amyloidosis Support Groups Inc.  
Wood Dale, Illinois

Angioma Alliance  
Norfolk, Virginia

Anxiety and Depression Association of  
America  
Silver Spring, Maryland

Aplastic Anemia & MDS International  
Foundation  
Rockville, Maryland

Arthritis Foundation  
Washington, District of Columbia

Association for Glycogen Storage Disease  
Durant, Iowa

Autoimmunity Research Foundation  
Thousand Oaks, California

AXYS  
Pine, Colorado

Breath of Hope, Inc  
Charlottesville, Virginia

Bridge the Gap - SYNGAP Education and  
Research Foundation  
Cypress, Texas

CADASIL Together We Have Hope Non-  
Profit  
Round Rock, Texas

Cancer Information & Support Network  
Auburn, California

Center for Medical Technology Policy  
Baltimore, Maryland

Childhood Arthritis & Rheumatology  
Research Alliance (CARRA)  
Durham, North Carolina

Children's PKU Network  
Encinitas, California

Choroideremia Research Foundation, Inc.  
Springfield, Massachusetts

Coalition Duchenne  
Newport Beach, California

Coalition for Pulmonary Fibrosis  
Los Angeles, California

Cutaneous Lymphoma Foundation  
Birmingham, Michigan

Dysautonomia International  
East Moriches, New York

Dyskeratosis Congenita Outreach, Inc.  
New York, New York

EveryLife Foundation for Rare Diseases  
Washington, District of Columbia

Fight Colorectal Cancer  
Washington, District of Columbia

Foundation for Prader-Willi Research  
Los Angeles, California

Friedreich's Ataxia Research Alliance  
(FARA)  
Annandale, Virginia

G-PACT  
Etters, Pennsylvania

Genetic Alliance  
Washington, District of Columbia

Global Genes  
Aliso Viejo, California

Global Healthy Living Foundation  
Upper Nyack, New York

Harvard Pilgrim Health Care Institute  
Boston, Massachusetts

HealthPartners Institute for Education and  
Research  
Minneapolis, Minnesota

Hepatitis Foundation International  
Silver Spring, Maryland

Hereditary Spherocytosis Society  
Hackensack, New Jersey

Hermansky-Pudlak Syndrome Network  
Oyster Bay, New York

HLRCC Family Alliance  
Boston, Massachusetts

ICAN, International Cancer Advocacy  
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In Need of Diagnosis, Inc. (INOD)  
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Inflammatory Breast Cancer Research  
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International Fibrodysplasia Ossificans  
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International Society for Mucopolysaccharidosis and  
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International WAGR Syndrome Association  
San Antonio, Texas

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Joubert Syndrome & Related Disorders  
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Louisiana PKU Alliance, Inc.  
Opelousas, Louisiana

Louisiana Public Health Institute  
New Orleans, Louisiana

Lupus and Allied Diseases Association, Inc.  
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Lymphatic Education & Research Network  
Glen Cove, New York

M-CM Network  
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March of Dimes  
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Myotonic Dystrophy Foundation  
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National ADrenal Diseases Foundation  
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Great Neck, New York

National Ataxia Foundation  
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National Gaucher Foundation, Inc.  
Harpers Ferry, West Virginia

National Health Council  
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National Organization for Rare Disorders  
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NBIA Disorders Association  
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NephCure Kidney International  
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Organic Acidemia Association  
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Parent Project Muscular Dystrophy  
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Parent to Parent USA  
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Patient Advocates In Research (PAIR)  
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PatientsLikeMe  
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Pediatric Congenital Heart Association  
Madison, Wisconsin

PFO Research Foundation  
Boulder, Colorado

Phelan-McDermid Syndrome Foundation  
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Powerful Patient  
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Prader-Willi Syndrome Association  
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Progeria Research Foundation  
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The Life Raft Group  
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The Marfan Foundation  
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The Praxis Project  
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