



4301 Connecticut Avenue, NW
Suite 404
Washington, DC 20008
202.966.5557
info@geneticalliance.org
<http://www.geneticalliance.org>

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who represent millions of patients and their families, researchers and clinicians, offer these comments on the Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care.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 We believe the draft guidance, intended to protect human subjects, will instead delay the development of critical information that can improve health, while affording minimal benefit to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
Network
Phoenix, Arizona

In Need of Diagnosis, Inc. (INOD)
Orlando, Florida

Inflammatory Breast Cancer Research
Foundation
West Lafayette, Indiana

International Fibrodysplasia Ossificans
Progressiva
Casselberry, Florida

International Society for Mucopolysaccharidosis and
Related Diseases
Saratoga, California

International WAGR Syndrome Association
San Antonio, Texas

John Paul II Medical Research Institute
Iowa City, Iowa

Joubert Syndrome & Related Disorders
Foundation
Mebane, North Carolina

Louisiana PKU Alliance, Inc.
Opelousas, Louisiana

Louisiana Public Health Institute
New Orleans, Louisiana

Lupus and Allied Diseases Association, Inc.
Verona, New York

Lymphatic Education & Research Network
Glen Cove, New York

M-CM Network
Chatham, New York

March of Dimes
Washington, District of Columbia

MLD Foundation
West Linn, Oregon

Myotonic Dystrophy Foundation
San Francisco, California

National ADrenal Diseases Foundation
(NADF)
Great Neck, New York

National Ataxia Foundation
Minneapolis, Minnesota

National Gaucher Foundation, Inc.
Harpers Ferry, West Virginia

National Health Council
Washington, District of Columbia

National Organization for Rare Disorders
(NORD)
Washington, District of Columbia

NBIA Disorders Association
El Cajon, California

NephCure Kidney International
King of Prussia, Pennsylvania

Organic Acidemia Association
Plymouth, Minnesota

Palo Alto Medical Foundation Research
Institute
Palo Alto, California

Parent Project Muscular Dystrophy
Washington, District of Columbia

Parent to Parent USA
Washington, District of Columbia

Patient Advocates In Research (PAIR)
Danville, California

PatientsLikeMe
Cambridge, Massachusetts

Pediatric Congenital Heart Association
Madison, Wisconsin

PFO Research Foundation
Boulder, Colorado

Phelan-McDermid Syndrome Foundation
Venice, Florida

Powerful Patient
Brookline, Massachusetts

Prader-Willi Syndrome Association
Sarasota, Florida

Progeria Research Foundation
Peabody, Massachusetts

Project DOCC - Delivery of Chronic Care
Great Neck, New York

PXE International
Washington, District of Columbia

Rare Disease Perspectives LLC
Sherborn, Massachusetts

Rare Genomics Institute
Bethesda, Maryland

RASopathies Network USA
Altadena, California

Rettsyndrome.org
Cincinnati, Ohio

Sage Bionetworks
Seattle, Washington

Sickle Cell Disease Association of America,
Inc.-Eastern NC Chapter
Jacksonville, North Carolina

Stanford University
Stanford, California

Stanford University IRBs
Stanford, California

StartCodon
Danville, California

Sysmark Information Systems Inc.
Rolling Hills Estates, California

The Empowered Patient Coalition
San Francisco, California

The Kanter Family Foundation
Palm Beach Gardens, Florida

The Life Raft Group
Wayne, New Jersey

The Marfan Foundation
Port Washington, New York

The Praxis Project
Washington, District of Columbia

The Sturge-Weber Foundation
Randolph, New Jersey

The Sudden Arrhythmia Death Syndromes
(SADS) Foundation
Salt Lake City, Utah

The United Leukodystrophy Foundation, Inc.
DeKalb, Illinois

Translational Genomics Research Institute
Phoenix, Arizona

Treuman Katz Center for Pediatric Bioethics
Seattle, Washington

Turner Syndrome Society of the United
States
Houston, Texas

University of Utah, Center for Clinical and
Translational Science
Salt Lake City, Utah

US Pain Foundation
Middletown, Connecticut

VHL Alliance
Boston, Massachusetts

Virginia Breast Cancer Foundation
Henrico, Virginia

We Are Curious, Inc.
Woodside, California

Individuals:

Jan Alderfer
Gluten Intolerance Group
Wichita Falls, Texas

Stephanie Alessi
Stanford Center for Biomedical Ethics
Stanford, California

Sheila Alexander
Pittsburgh, Pennsylvania

Stephanie Allen
Akron Children's Hospital
Akron, Ohio

Ronald Ariagno
Stanford University
Stanford, California

Paul Avillach
Harvard Medical School – CBMI
Boston, Massachusetts

Julie Bass
American Occupational Therapy Foundation
Bethesda, Maryland

Alan Beggs
Boston Children's Hospital / Harvard
Medical School
Boston, Massachusetts

Deacon John Berstecher
Laurel Springs, New Jersey

Geraldine Bliss
Phelan-McDermid Syndrome Foundation
Houston, Texas

Murray Brilliant
Marshfield Clinic Research Foundation
Marshfield, Wisconsin

Wylie Burke
University of Washington
Seattle, Washington

Lynn Bush
Columbia University Medical Center
New York, New York

David Christiani
Massachusetts General Hospital
Boston, Massachusetts

M. Wayne Clark
Private Practice Marriage and Family Thp.
and Pastoral Therapist
Ankeny, Iowa

Nadine Cohen
Blue Note Biosciences
Princeton, New Jersey

Laurel Copeland
Baylor Scott & White Health
Temple, Texas

Marty Crawford
Michigan State University
East Lansing, Michigan

Sandra Daack-Hirsch
University of Iowa College of Nursing
Iowa City, Iowa

Edith Dekel
Maccabi Institute for Health Services
Research
Tel Aviv, Israel

Edward De Vol
Infinity Limited
Dallas, Texas

Patricia Engelhard
Senhoc
Lincoln, Nebraska

Ruth Faden
Berman Institute of Bioethics
Baltimore, Maryland

Lisa Feuchtbaum
Research Scientist
Berkeley, California

Bela Fishbeyn
Stanford Center for Biomedical Ethics
Stanford, California

Dawn Frazier
Ovarian Cancer Patient
Travelers Rest, South Carolina

Cindy Geoghegan
Patient & Partners
Madison, Connecticut

Matthew Gillman
Harvard Medical School
Boston, Massachusetts

Michael Gould
Department of Research and Evaluation,
Kaiser Permanente Southern California
Pasadena, California

Margaret Haas
Retired RN
Fort Pierce, Florida

Deborah Hamm, MD
Faculty member of Columbia University
Medical Center
New York, New York

Lisa Helms Guba, RN, Lt Col USAF
Dyskeratosis Congenita Outreach, Inc
Annapolis, Maryland

Sean Hennessy
University of Pennsylvania
Philadelphia, Pennsylvania

Susan Huang
University of California Irvine Health
School of Medicine
Irvine, California

Kevin Hughes
Hughes RiskApps, LLC
Boston, Massachusetts

Jessica Illuzzi
Yale University
New Haven, Connecticut

Gail Jarvik
University of Washington Dept of Medicine
(Medical Genetics)
Seattle, Washington

Nancy Kass
Berman Institute of Bioethics
Baltimore, Maryland

Devon Kelly
Knight Cancer Institute
Portland, Oregon

Stephen Kingsmore
Children's Mercy - Kansas City; University
of Missouri - Kansas City
Kansas City, Missouri

Barbara LeStage
Dana Farber/Harvard Cancer Center Breast
Cancer Advocates
Wrentham, Massachusetts

Diedra Levi
The Living Affected Corporation
North Little Rock, Arizona

Michele Lloyd-Puryear
Takoma Park, Maryland

Edward Lose
UAB Genetics
Birmingham, Alabama

Jeantine Lunshof
Harvard Medical School
Boston, Massachusetts

David Magnus
Stanford Center for Biomedical Ethics
Stanford, California

Gail Marcus
DHHS
Wilmington, North Carolina

Gail Marcus
Public Health Genetics
Wilmington, North Carolina

Amy McGuire
Baylor College of Medicine
Houston, Texas

Lindsey Mette
UTHSCSA
San Antonio, Texas

Thomas Moulton, MD
Bronx SCAHN
Bronx, New York

Bernard Munos
FasterCures; and
InnoThink Center for Research in
Biomedical Innovation
Indianapolis, Indiana

Lynda Nelson
FORCE
James City, Pennsylvania

Linda Nichols
Desoto, Texas

Robert Nussbaum
University of California San Francisco
San Francisco, California

David Oakes
Stanford University
Stanford, California

Selassie Ogyaadu
BronxScan
Bronx, New York

Sanjay Patel
Brigham and Women's Hospital
Brookline, Massachusetts

Nathaniel Pearson
New York Genome Center
New York, New York

Nancy Reame
Columbia University
New York, New York

Susan Redline
Brigham and Women's Hospital
Boston, Massachusetts

Lainie Ross
University of Chicago
Chicago, Illinois

Sandra Schaffner
Oceanside, California

Christopher Scott
Stanford Center for Biomedical Ethics
Stanford, California

Matthew Smith
Joubert Syndrome & Related Disorders
Foundation
Mebane, North Carolina

Julian Solway
University of Chicago Institute for
Translational Medicine
Chicago, Illinois

Erika Spaeth
Gene By Gene, Ltd
Houston, Texas

Phyllis Speiser
Cohen Children's Medical Center of New
York; Hofstra-North Shore LIJ School of
Medicine
Lake Success, New York

David Spiegel, M.D.
Stanford University School of Medicine
Stanford, California

Nathan P. Thomas, Sr.
Silver Spring, Maryland

Ella Thompson
HMO Research Network
Seattle, Washington

Sarita Wahba
PCORI
Washington, District of Columbia

Alexander Walker
World Health Information Science
Consultants
Newton, Massachusetts

Rainne Wells
AF Sergeants' Association
Weogufka, Alabama

Todd Whitehurst, M.D.
Cupertino, California

Benjamin Wilfond
Seattle Children's Research Institute
Seattle, Washington

Darrell Wilson
Stanford University
Stanford, California

Michael Mingzhao Xing
Johns Hopkins University School of
Medicine
Baltimore, Maryland

Barbara Zedler
Venebio Group, LLC
Richmond, Virginia

Steven Ziemba
Marshfield Clinic Research Foundation
Marshfield, Wisconsin