

IRB Review of Multi-Site Pediatric Clinical Research Protocols

Steven Hirschfeld, MD PhD

Captain, U.S. Public Health Service

Associate Director for Clinical Research

Eunice Kennedy Shriver National Institute of Child Health and
Human Development

NIH Co-Coordinator, CTSA Consortium Child Health Oversight
Committee

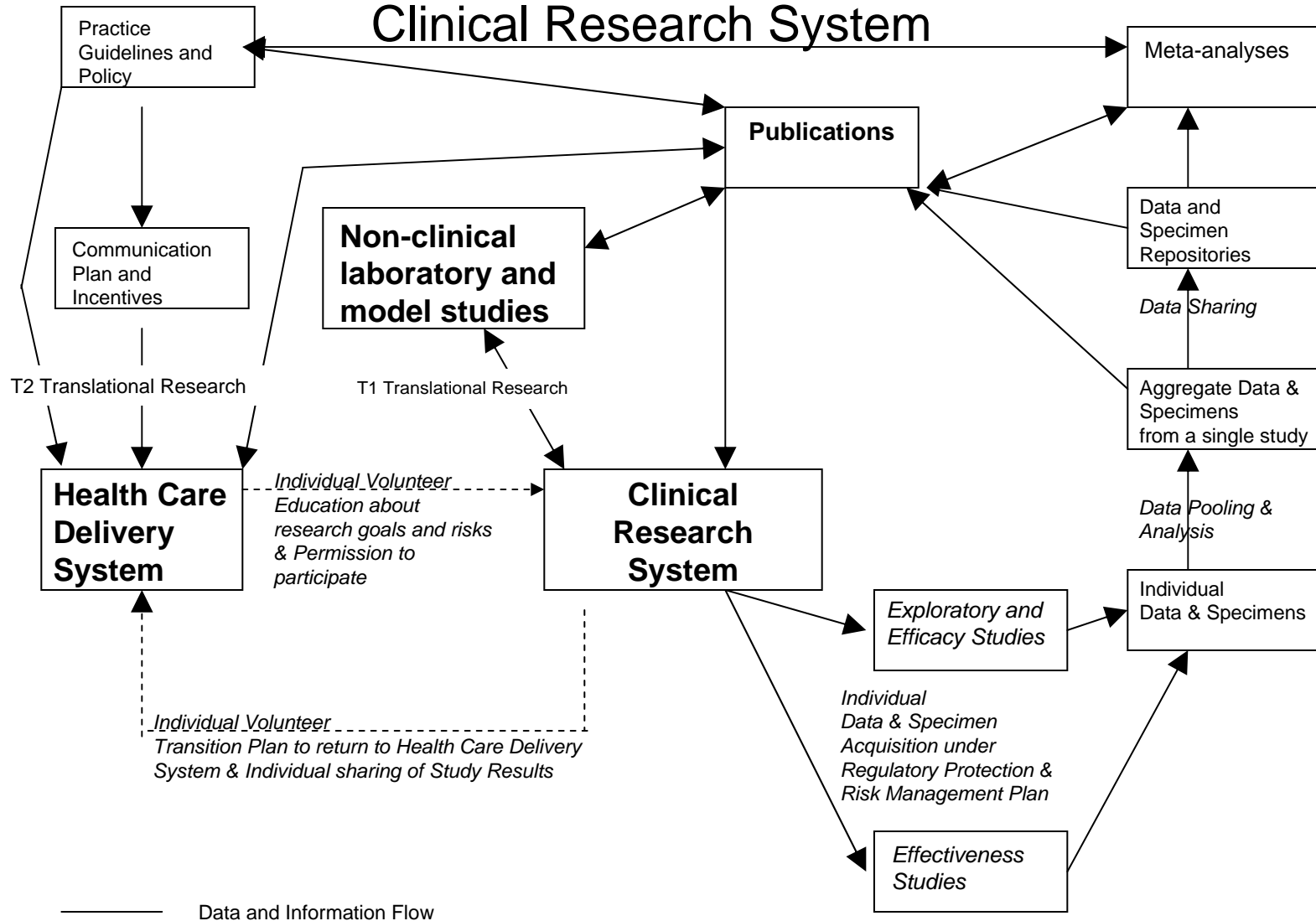
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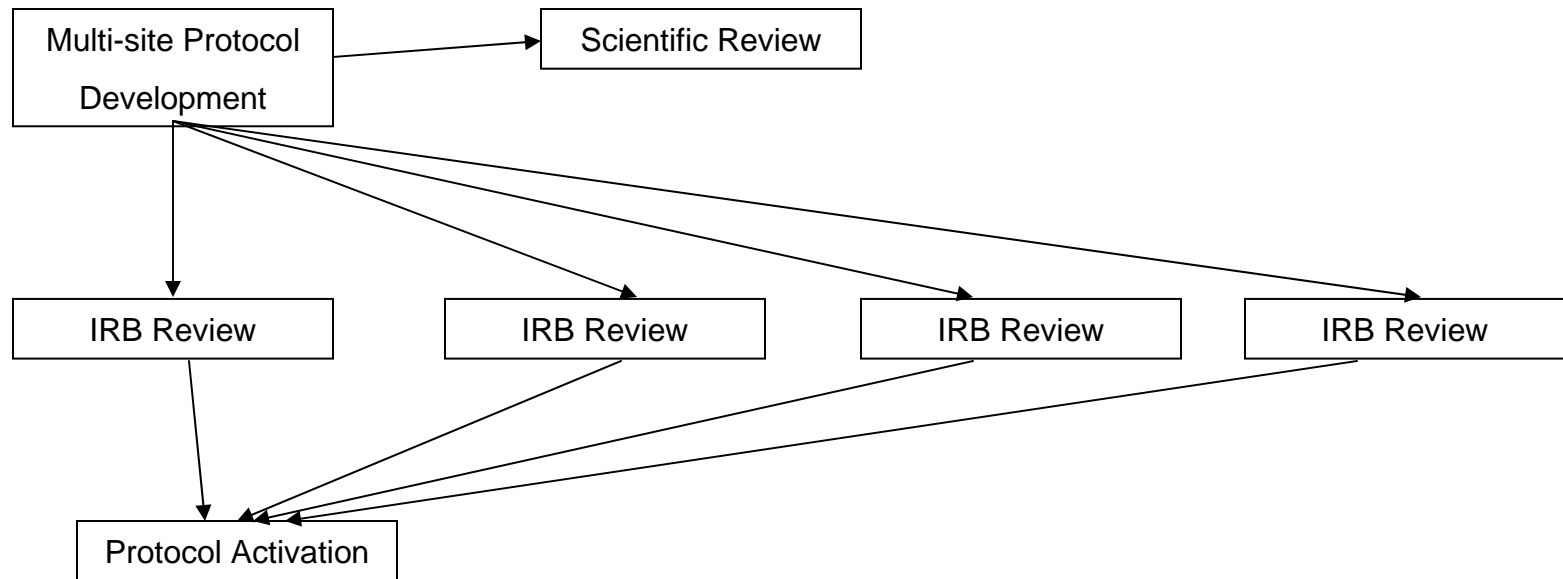
Framing the context

- ▶ Pediatric multi-site research has been actively supported by the Federal government for about a half a century
- ▶ Harmonization and synchronization for protocol implementation is a fundamental principle of multi-site studies
- ▶ Data coordination through dedicated centers and data transmission, analysis and acquisition standards through electronic records and data management have evolved over the last decade
- ▶ Human subject protections have regulations and policies but by design have local interpretation and implementation

Interaction between Health Care Delivery System and Clinical Research System



Protocol Development



Multi-site IRBs and Pediatric Clinical Studies

- ▶ Challenges in IRB review of multi-site pediatric clinical studies
 - Temporal delays to reach study activation and accrual targets
 - Inconsistencies in review

Different risk categories

Different stipulations

Different eligibility

Different types of review incorporating scientific and statistical consideration in IRB process

NICHD Clinical Research

- ▶ About 60 networks and consortia are partially or completely supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- ▶ About 2000 projects at about 500 sites in about 27 countries with about a \$ 650 million budget
- ▶ Wide scope of populations including some of the most vulnerable including fetuses, newborns, pregnant women, children, adolescents, rehabilitation patients, and people with disabilities, rare diseases and genetic syndromes
- ▶ For multi-site studies reports of inconsistencies and study delays attributed to IRBs are received regularly by NICHD scientists

<http://www.nichd.nih.gov>

Clinical and Translational Science Awards (CTSA)

- ▶ National Center for Research Resources has responsibility for NIH Roadmap derived program to develop a national infrastructure for clinical and translational research
- ▶ About 40 awards have been made to academic institutions to become CTSA sites
- ▶ CTSA program includes a mandate to support clinical and translational research in children
- ▶ CTSA Consortium Child Health Oversight Committee (CC-CHOC) develops child health oriented initiatives and advises the overall CTSA Consortium Steering Committee
- ▶ CC-CHOC has scheduled meetings and subcommittees, which have consistently identified inconsistencies and study delays by IRB review of multi-site studies as a barrier to pediatric clinical research

<http://www.ctsaweb.org>

CTSA-NICHD Workshop September 11, 2007

- ▶ Highlight some of the challenges in assessing pediatric research proposals;
- ▶ Build a culture of harmonization and trust among institutions involved with pediatric research;
- ▶ Demonstrate the feasibility of multi-institutional teams to communicate and collaborate to reach common objectives.
- ▶ Hypothetical case discussions to address potential IRB issues with pediatric studies
- ▶ All IRB representatives on case study panels were actual IRB members from NIH funded study sites.

Case Study 1: Maintenance therapy for Systemic Lupus Erythematosus (SLE)

▶ **Moderator:** Nancy Bridges, NIH/NIAID

▶ **Panelists:**

- Diane Wara, University of California, San Francisco, Pediatric Immunologist
- John Falletta, Duke University, Pediatric Hematologist and Oncologist, Senior IRB chairman
- Hank Mayer, University of Pennsylvania, Pediatric Pulmonologist
- Barbara LoDico, University of Pennsylvania, Director of Human Subject Research
- Tony Perez, University of California, Davis, IRB Director
- Elizabeth Steiner, Oregon Health and Sciences University, IRB Member

Case Study 2: Insulin Clamp, Body Mass Index (BMI) and Risk of Diabetes

▶ **Moderator:** Victoria Pemberton, NIH/NHLBI

▶ **Panelists:**

- Sandra Alfano, Yale School of Medicine, IRB Chair
- Silva Arslanian, University of Pittsburgh, Professor of Pediatrics, Director of Pediatric Clinical and Translational Research Center (CTSA)
- Sandy Vasan, The Rockefeller University, Pediatric Consultant to IRB
- Lisa Teot, University of Pittsburgh, Pediatric Pathologist & Scientific IRB Member
- Richard Guido, University of Pittsburgh, IRB Chairman, Magee-Women's Hospital
- David Asmuth, University of California, Davis, IRB Chair

Case Study 3: Screening for autism spectrum disorders in infants

▶ **Moderator:** Rosemary Higgins, NIH/NICHD

▶ **Panelists:**

- Michael Cotten, Duke University
- Allyn McConkie-Rosell, Duke University
- Kathleen Kennedy, University of Texas
- Benjamin Handen, University of Pittsburgh
- Richard Guido, University of Pittsburgh
- Sudha Kashyap, Columbia University

Case Study 4: Gene therapy for glioblastoma multiforme

▶ **Moderator:** Malcolm Smith, NIH/NCI (Pediatric Oncologist)

▶ **Panelists:**

- Seymour Zoger, MD; University of California, San Francisco (Pediatric Oncologist, Vice-Chair UCSF IRB)
- Carola Arndt, MD; Mayo Clinic (Pediatric Oncologist, former IRB member)
- Melody J. Sacatos, CIP; Yale University (Manager of Protocol Development and formerly head of Compliance for the Yale IRB)
- Nicholas Ferrario, University of Rochester (Director of Operations & Regulatory Affairs)
- Mary Adams, University of Rochester (Executive Director, University of Rochester IRB)
- Carl D'Angio, MD; University of Rochester (Neonatology; Director, Pediatric Clinical Research Office)
- David Korones, MD; University of Rochester (Pediatric Oncologist)

Case Study 5: Emergent intervention for treatment of self inflicted injury

▶ **Moderator:** Cheryl Boyce, NIH/NIMH

▶ **Panelists:**

- Tom McMahon, Yale University
- Barry Mangum, Duke University
- David Asmuth, University of California, Davis
- Tony Perez, University of California, Davis
- Susan Bankowski, Oregon Health and Science University
- John Ennever, Columbia University.

September 11, 2007 Workshop Follow Through

- ▶ The conference was recorded and archived on the NIH CTSA website at <https://webmeeting.nih.gov/p37176252/>
- ▶ Proof of concept demonstrated that IRB members from different institutions can reach consensus on challenging issues
- ▶ A national pediatric IRB consult group was formed

NCRR-NICHD Workshop/Webinar on April 23, 2009

Purpose: Learn in a structured manner about different models for IRB evaluation of multisite pediatric clinical research protocols.

April 23, 2009 Multi Site Pediatric Study IRB Workshop/Webinar: Discussions were provided Points to Consider

- ▶ Required resources for IRB to function properly
- ▶ Availability of pediatric expertise on IRB- permanent or ad hoc
- ▶ Average time for protocol review
- ▶ Range of time for protocol review
- ▶ Proportion of protocols that proceed without major revisions
- ▶ Proportion that have specific stipulations that require major revisions before proceeding with enrollment
- ▶ Monetary cost for protocol review and who pays
- ▶ Opportunities and policies to consult with other IRBs
- ▶ Level of interaction with local site IRBs for multi site studies
- ▶ Process for addressing local site IRB amendments or stipulations
- ▶ Process for safety monitoring (central- delegated-both?) for multi site studies

Central IRB Panel

- ▶ Jaci Goldberg, JD, Administrator, Central Institutional Review Board, National Cancer Institute
- ▶ K. Lynn Cates, MD, Assistant Chief Research & Development Officer, Director, Program for Research Integrity Development & Education (PRIDE), Office of Research & Development, Department of Veterans Affairs
- ▶ Naynesh Kamani, MD, Chair, Institutional Review Board, Medical Director, Office for the Protection of Human Subjects, Principal Investigator, Children's Research Institute, Center for Cancer and Immunology Research Children's National Medical Center; George Washington University
- ▶ Stacey Berg, MD, Professor, Department of Pediatrics, Section of Hematology/Oncology, Baylor College of Medicine, Associate Dean for Research Assurances, Baylor College of Medicine, Director of Clinical Research, Texas Children's Cancer Center Baylor College of Medicine;
- ▶ Stephen Davis, MD, Chair, Department of Pediatric Critical Care Medicine, Cleveland Clinic;
- ▶ Daniel Nelson, MS CIP, Associate Professor of Social Medicine and Pediatrics, and Director, Office of Human Research Ethics at the University of North Carolina-Chapel Hill

Reciprocal IRB Agreement Panel

- ▶ Michele Russell-Einhorn, JD, Director, Office for Protection of Research Subjects, Dana-Farber Harvard Cancer Center
- ▶ Alison Lakin RN, LL.B, LL.M, Ph.D, Director, COMIRB and HSRC, University of Colorado,
- ▶ Theresa O'Lonegan, Research Subject Advocate, Pediatric Clinical Translational Research Center, University of Colorado
- ▶ Keith C. Norris, MD, Professor of Medicine and Executive Vice President of Research & Health Affairs at Charles Drew University of Medicine and Science in Los Angeles, California

Rotating IRB Panel

- ▶ J. Michael Dean, MD, MBA, H.A. and Edna Benning Professor of Pediatrics, University of Utah
- ▶ Carol E. Nicholson, MD, MS, FAAP, Project Scientist, Collaborative Pediatric Critical Care Network (CPCCRN), Program Director, Pediatric Critical Care and Rehabilitation Research (PCCR)
- ▶ John Stillman, CIP, Director, Institutional Review Board, University of Utah;
- ▶ Sally Jo Zuspan, RN, MSN, Program Manager & Research Specialist for the Pediatric Emergency Care Applied Research Network University of Utah;
- ▶ Ronald F. Maio, D.O., M.S., Professor, Department of Emergency Medicine Director of the Office of Human Research Compliance Review, University of Michigan
- ▶ James Chamberlain, MD Division Chief, Emergency Medicine Children's National Medical Center George Washington University;
- ▶ Dan Kavanaugh, MSW, LCSW-C, Captain, U.S. Public Health Service, Senior Program Manager, HRSA/MCHB Emergency Medical Services for Children Program

Commercial IRB Panel

- ▶ Stephen J. Rosenfeld, M.D., M.B.A. President and Chief Executive Officer, Western Institutional Review Board
- ▶ David G. Forster, J.D., M.A., C.I.P, Vice President of Compliance, Western Institutional Review Board
- ▶ Raffaella Hart, CIP, CIM, Director of the BRANY IRB
- ▶ James Saunders, MBA, Vice President and Director of Business Development, New England IRB
- ▶ Theresa M. Straut, BA, CIP, RAC (US), Executive Director, IRB Services Chesapeake Research Review, Inc.
- ▶ Amy L. Schwarzhoff, BS, CIP, Executive Director, Consulting and Research Chesapeake Research Review, Inc.
- ▶ Jonathan M. Davis, MD, Professor of Pediatrics, Tufts University

Discussion Panel

- ▶ Alexander A. Kon, MD Associate Professor, Pediatrics and Bioethics, Director, Clinical Bioethics Consultation Service, Chair, Bioethics Consultation Committee, Director, Bioethics Clinical and Translational Science Center
- ▶ Robert "Skip" Nelson, MD PhD, Pediatric Ethicist, Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration
- ▶ Debbie S. Gipson, MD, Associate Professor of Medicine and Pediatrics, University of North Carolina, Chapel Hill
- ▶ Vicki Pemberton, RNC, MS, CCRC , National Heart Lung and Blood Institute
- ▶ Theresa O'Lonergan, Research Subject Advocate, Pediatric Clinical Translational Research Center, University of Colorado
- ▶ Francis P. Crawley, MA, FFPM, Executive Director, Good Clinical Practice Alliance-Europe;
- ▶ Julie Kaneshiro MA and Ivor Pritchard, PhD, Office for Human Research Protections
- ▶ Lainie Friedman Ross, MD, PhD Carolyn and Matthew Bucksbaum Professor of Clinical Ethics Professor, Departments of Pediatrics, Medicine, and Surgery, Associate Director, MacLean Center for Clinical Medical Ethics, University of Chicago

April 23, 2009 IRB Model Workshop/Webinar Summary

Primary Features of IRB models

- ▶ Central IRB- facilitated review at institutions with reciprocal agreement.
- ▶ Reciprocal agreement- multiple variations on common theme of mutual recognition of primary review plus ongoing information exchange among institutions that are aligned geographically or administratively within a system.
- ▶ Rotating IRB- Lead IRB provides review and review is communicated by investigators with performance tracking to other institutions.
- ▶ Commercial IRB- Variations on a theme of outsourcing IRB functions.

April 23, 2009 IRB Model Workshop/Webinar Summary

Panel discussion noted

- ▶ Recognition of cultural and perceptual differences between institutions of eligibility, risk, consent and assent process, regulatory interpretation
- ▶ Various models relay on general process communication between parties formalized through legal agreements. Generally no dynamic communication or information exchange during review process.

April 23, 2009 Workshop/Webinar Follow through

- ▶ The conference was recorded and archived on NIH website <http://videocast.nih.gov/Summary.asp?File=15053>
- ▶ Development of a pilot project using a federation model to be implemented and assessed at selected CTSA sites

Proposed Federation Model

- ▶ Member IRBs sign on to a compact that outlines principles, process and performance standards for review of multi-site pediatric studies
- ▶ Knowledge of principles, process and performance can build consistency and trust
- ▶ Trust will minimize risk mitigation procedures and resources
- ▶ Consistency will facilitate review process
- ▶ Initial pilot will be in CTSA sites that volunteer to implement and evaluate the pilot with opportunities for dynamic changes during the pilot

Proposed Federation- Principles

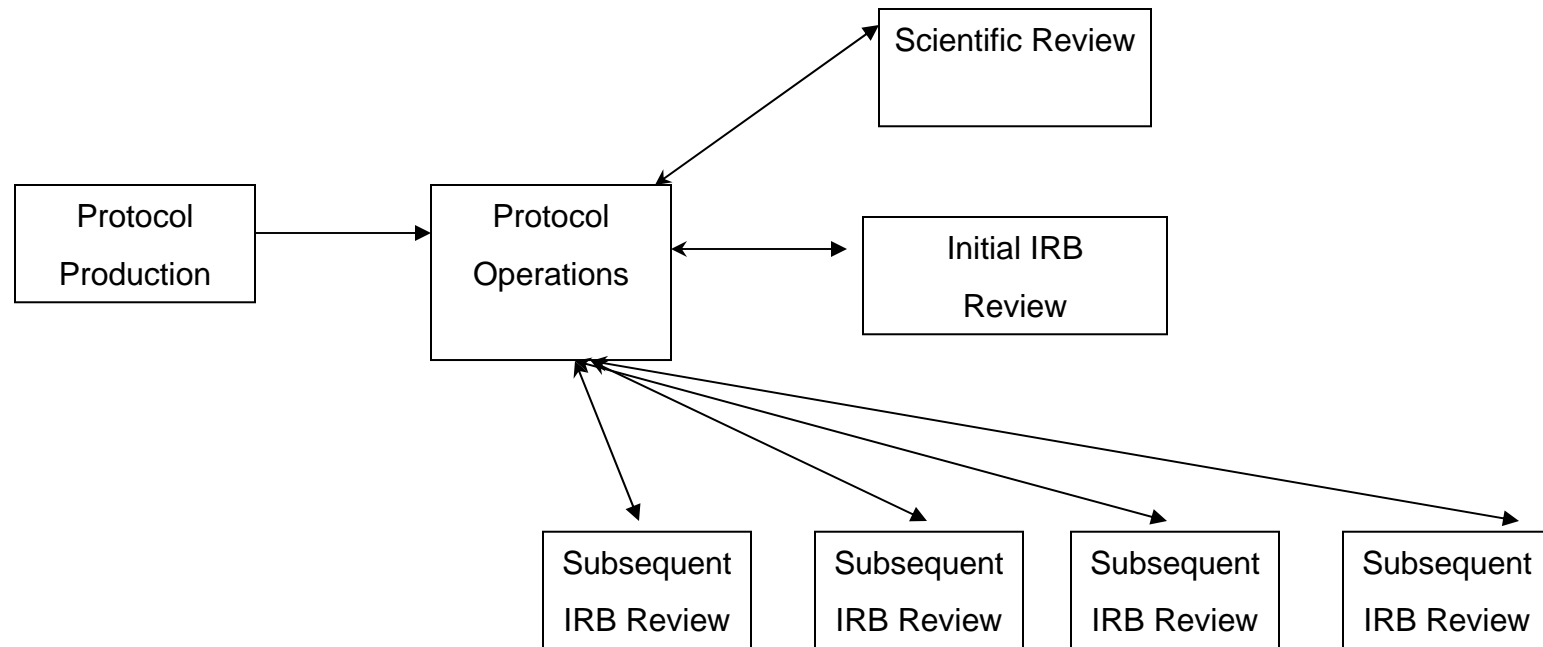
- ▶ Recognition that the responsibility of an IRB is for human subject protection
- ▶ Compliance with pertinent regulations such as 45CFR46 and 21CFR50 and guidance documents such as ICH E6 and ICH E11
- ▶ Recognition that variations are possible in the circumstances of when permission, assent and consent are required and when either the initial process can be waived for emergency research or when parental permission can be waived for certain infectious diseases or psychiatric conditions
- ▶ Recognition that data sharing is a goal and that the permission, assent and consent process should anticipate future uses of data and specimens
- ▶ Recognition that outcome measures and assessments should be population specific
- ▶ Recognition of a hierarchy of evidence in making extrapolations and interpreting data for risk assessment
- ▶ Recognition that assessment schedules should accommodate families and be age appropriate
- ▶ Recognition that safety monitoring is context dependent

Proposed Federation- Process

- ▶ Health care providers with experience with the population of interest and the condition of interest should be part of the review
- ▶ Local experience should be an important determinant of risk so data regarding local experience with assessments and interventions should be available. Absent adequate local data, literature should be used to guide risk determination
- ▶ Criteria for supplemental monitoring such as a recommendation for an Independent Data Monitoring Committee should be proactively developed
- ▶ Communication plan between relevant parties such as investigators, institutional offices, sponsors, funding organizations and regulatory authorities should be proactively developed
- ▶ Information regarding other competent assessments of a proposed study, for example other IRBs or review groups, should be shared
- ▶ Definitions of responsibilities among review parties such as Scientific Review Group, Independent Data Monitoring Committee and IRB should be clarified

Proposed Federation- Process Map

Multisite protocols within the Federation are coordinated by an Operations Center that clears in sequence Scientific Review, Initial IRB Review and Subsequent IRB Reviews. All the reviews and responses from the Protocol Production Team are included in the package for subsequent submissions. The last IRB to review the protocol may receive the protocol with reviews from the Initial IRB and multiple other IRBs



Proposed Federation- Performance

- ▶ Logistics of protocol distribution from protocol development team will be handled by a Protocol Coordinator at a Protocol Operations Center
- ▶ IRB review will follow Scientific Review
- ▶ For initial review of a study, first IRB will review in one cycle based on regularly scheduled meetings
- ▶ IRB summary review of the initial IRB review will be attached to protocol package for delivery to subsequent IRBs
- ▶ Subsequent IRB review of a study already approved by a recognized IRB within the Federation will occur in one cycle based on regularly scheduled meeting. Review may be abbreviated
- ▶ Each subsequent IRB summary review will be attached to protocol package for delivery to Protocol coordinator to maintain a composite file of all comments
- ▶ Any changes in perception of risk category or approvability will be communicated to all IRBs by Protocol Coordinator upon receipt of assessment
- ▶ Protocol amendments will follow the same process of initial IRB review and subsequent distribution to other IRBs
- ▶ Tracking of time from submission to distribution to action will be kept by Protocol Coordinator

Next Steps

- ▶ Request for Information issued by NIH
- ▶ Pilot programs to begin estimated 4th quarter calendar year 2009
- ▶ Program to be evaluated at 90 day intervals
- ▶ Expansion or modification of program as informed by evaluations