Clinical Research Networks: Building the Foundation for Heath Care Transformation

May 8, 2008

Natcher Conference Center
National Institutes of Health
45 Center Drive
Bldg 45, Auditorium
Bethesda, Maryland 20892

This Program is funded by the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and the U.S Department of Health and Human Services (DHHS). The project is one of the initiatives under the NIH Roadmap for Medical Research, a series of far-reaching initiatives designed to transform the Nation's medical research capabilities and speed the movement of research discoveries from the bench to the bedside

National Center for Research Resources

Clinical Research Computing Unit

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8:15 A.M. ***Registration (outside Auditorium) and Poster Session (Balcony Level)***

9:00 A.M. ***Welcome and Introductions Dr. Barbara Alving, Director NCRR, NIH***

9:15 A.M. ***Case Studies 1:***
Clinical Research Informatics and Interoperability
Dr. Lee Green, Dr. Kevin Peterson, Dr. J. Richard Landis

Case Studies 1 Moderators:
Dr. Jonathan C. Silverstein, U Chicago
Dr. Christopher G. Chute, Mayo Clinic

10:30 A.M. ***Plenary Session 1: Keynote Address Dr. Elias Zerhouni, Director NIH***
Integrating & Expanding Research Networks to Transform the Clinical Research Enterprise

10:50 A.M. ***Break and Demos (Balcony Rooms A, B, C) and Room H (outside Auditorium)***

11:00 A.M. ***Case Studies 2:***
Integrative Informatics in Support of Translational Research:
Dr. James Kahn, Dr. Gregory Reaman, Dr. Dennis L. Confer

Case Studies 2 Moderators:
Dr. P. Jon White, Health IT Director, AHRQ
Dr. M. Edwina Barnett, DTCC Program Director, RCMI Translational Research Network

12:00 P.M. ***Poster Session (Balcony) and Lunch (Natcher Cafeteria)***

1:00 P.M. ***Plenary Session 2: Keynote Address Dr. Isaac Kohane, Harvard Med School***
Transforming the Clinical Research Enterprise

2:00 P.M. ***Case Studies 3:***
Reducing Barriers to Research
Dr. Carol Dukes Hamilton, Dr. Stephen B. Johnson, Dr. Alan H. Morris

Case Studies 3 Moderators:
Dr. Francis Chesley, Director OEREP, AHRQ
Loretta Jones, M.A., Executive Director Healthy African American Families
Dr. John Hickner, Family Medicine, U Chicago

3:00 P.M. ***Break and Demos (Balcony Rooms A, B, C) and Room H (outside Auditorium)***

3:20 P.M. ***Case Studies 4:***
Disseminating Knowledge into Practice
Dr. Robert Harrington, Dr. Eric B. Larson, Dr. Robert Williams, Ms. Nancy Dianis

Case Studies 4 Moderators:
Dr. Philip J. Baty, Advantage Health Physician Network
Dr. David Meyers, AHRQ CP3 Director

4:20 P.M. ***Closing Remarks Dr. Barbara Alving, Director NCRR, NIH***

5:00 P.M. ***Demos (Balcony Rooms A, B, C) and Room H (outside Auditorium)***
Poster Session (Balcony)

5:30 P.M. ***Adjournment***

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ACKNOWLEDGEMENTS

The Roadmap Steering Committee wishes to thank the members of the Planning Committee for their assistance and guidance in the preparation of this meeting.

The Roadmap Planning Committee acknowledges with grateful thanks the leadership and support provided by the Co-Chairs of the Planning Committee, Lee Green, M.D. and James Kahn, M.D.

We are highly appreciative of the valuable time and effort extended by the panel moderators in critical review of the investigator case studies and the expert analysis and input provided on the many issues confronting the clinical research networks.

The Investigators of the Roadmap Clinical Research Networks wish to extend special thanks and great appreciation to Dr. Jody Sachs for her devotion and unwavering support of the Roadmap programs.

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PLANNING COMMITTEE

Elaine S. Collier, M.D.
Assistant Director for Clinical Research
Division of Clinical Research Resources
National Center for Research Resources

Lee Green, M.D., M.P.H.
Professor & Associate Chair for
Information Management
University of Michigan Family Medicine Office

James Kahn, M.D.
Professor of Medicine
University of California, San Francisco

David C. Lanier, M.D.
Associate Director of CP3
Agency for Healthcare Research & Quality

Donna J. McCloskey, Ph.D.
Health Scientist Administrator
Division of Clinical Research Resources
National Center for Research Resources

Dr. Shelia A. McClure, Ph.D
Director, RCMI Program
Division of Research Infrastructure
National Center for Research Resources

Rosemary A. Madigan, M.S., M.P.H.
Manager, Project Operations & Compliance
University of Pennsylvania School of Medicine

Jody G. Sachs, D.P.M.
NIH Roadmap Scientific Project Officer
Division of Clinical Research Resources
National Center for Research Resources

Michael H. Sayre, Ph.D.
IDeANet Program Officer
Division of Research Infrastructure
National Center for Research Resources

Douglas M. Sheeley, Sc.D.
Health Scientist Administrator
Division of Biomedical Technology
National Center for Research Resources

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SPEAKERS AND MODERATORS

Speakers

Barbara M. Alving, MD
***Director,* National Center for Research Resources**
National Institutes of Health

Dr. Barbara M. Alving is the Director of the National Center for Research Resources (NCRR) at the National Institutes of Health. NCRR provides laboratory scientists and clinical researchers with the environments and tools they need to understand, detect, treat, and prevent a wide range of common and rare diseases.

Dr. Alving earned her medical degree cum laude from Georgetown University School of Medicine, where she also completed an internship in internal medicine. She received her residency training in internal medicine at the Johns Hopkins University Hospital, followed by a fellowship in hematology. Dr. Alving then became a research investigator in the Division of Blood and Blood Products at the Food and Drug Administration. In 1980, she joined the Department of Hematology at the Walter Reed Army Institute of Research and became Chief of the Department in 1992. She left the Army at the rank of Colonel in 1996 to become the Director of the Medical Oncology/Hematology section at Washington Hospital Center in Washington, D.C. In 1999, she joined the National Heart, Lung, and Blood Institute (NHLBI), serving as the Director of the extramural Division of Blood Diseases and Resources until becoming the Deputy Director of the Institute in September 2001. From September 2003 until February 1, 2005, she served as the Acting Director of NHLBI. In March 2005 she became the Acting Director of NCRR and was named Director in April 2007.

Dr. Alving is a Professor of Medicine at the Uniformed Services University of the Health Sciences in Bethesda, a Master in the American College of Physicians, a former member of the subcommittee on Hematology of the American Board of Internal Medicine, and a previous member of the FDA Blood Products Advisory Committee. She is a co-inventor on two patents, has edited three books, and has published more than 100 papers in the areas of thrombosis and hemostasis.

Alan M. Krensky, MD

Alan M. Krensky, MD, is the first Director of the Office of Portfolio Analysis and Strategic Initiatives (OPASI) and a Deputy Director of the National Institutes of Health. For the past 23 years, he was at Stanford University, where he served as the Shelagh Galligan Professor of Pediatrics, Associate Dean for Children's Health, Associate Chair for Research, Chief of the Division of Immunology and Transplantation Biology, and Executive Director of the Children's Health Initiative. A medical graduate of the University of Pennsylvania in 1977, he trained in pediatrics and nephrology at Boston Children's Hospital and immunology at Dana-Farber Cancer Institute. After one year on the faculty at Harvard University, he moved to Stanford as Assistant Professor of Pediatrics in 1984. He was appointed Shelagh Galligan Professor in 1995 and has been at NIH since July 8, 2007.

Dr. Krensky is a member of the American Society of Clinical Investigation, Association of American Physicians, Society for Pediatric Research, American Pediatric Society, and American Association of Immunologists. As Executive Director of the Children's Health Initiative and Associate Dean for Children's Health at Stanford, Dr. Krensky planned and implemented a $500 million investment in preeminence and sustainability of the Lucile Packard Children's Hospital at Stanford. He helped develop six centers of excellence, five multidisciplinary cores, and the recruitment of more than 40 faculty.

Dr. Krensky's research program was continuously funded by the National Institutes of Health from 1984 to his assumption of the NIH post. He has made important contributions to understanding the role of human T lymphocytes in human disease and applying this information to the development of new diagnostic and therapeutic approaches to disease. He first identified the human lymphocyte function-associated antigens (1-3), the chemokine RANTES, the host defense molecule granulysin, and the transcription factor KLF-13 (RFLAT-1). He has published more than 250 scientific articles and reviews, holds nine patents, and has served on many editorial and scientific review boards.

Isaac (Zak) Kohane, MD
***Director*, Children's Hospital Informatics Program**
***Henderson Professor of Pediatrics & Health Sciences & Technology,* Harvard Medical School (HMS)**
***Co-Director*, HMS Center for Biomedical Library**
***Director*, HMS Countway Library of Medicine**

Isaac (Zak) Kohane is the director of the Children's Hospital Informatics Program and is the Henderson Professor of Pediatrics and Health Sciences and Technology at Harvard Medical School (HMS). He is also the co-Director of the HMS Center for Biomedical Library and Director of the HMS Countway Library of Medicine. Dr. Kohane leads multiple collaborations at Harvard Medical School and its hospital affiliates in the use of genomics and computer science to study cancer and the development of the brain (with

emphasis on autism). He also has developed several computer systems to allow multiple hospital systems to be used as "living laboratories" to study the genetic basis of disease while preserving patient privacy.

Dr. Kohane has published over 160 papers in the medical literature and authored a widely used book on Microarrays for an Integrative Genomics. He has been elected to multiple honor societies including the American Society for Clinical Investigation and the American College of Medical Informatics. He leads a doctoral program in genomics and bioinformatics at MIT. He is also a practicing pediatric endocrinologist and father of three energetic children.

Moderators

M. Edwina Barnett, MD, PhD, MBA, FACP

M. Edwina Barnett, MD, PhD, MBA, FACP is the Program Director at the Data Technology Coordinating Center for the Research Centers in Minority Institutions (RCMI) Translational Research Network (RTRN). RTRN is a cooperative research network that facilitates translational research in health disparity areas.

Dr. Barnett received her medical degree from the Johns Hopkins University School of Medicine. She completed her internal medicine residency at the Cleveland Clinic Educational Foundation and University Hospitals of Cleveland. A fellowship in nephrology and hypertension was also done at University Hospitals of Cleveland followed by a Ph.D. in cellular and molecular biology at Case Western Reserve University.

She had a private practice at Arnett Clinic in Lafayette, Indiana for seven years during which she also served as Associate Dean for Research & Graduate Studies in the School of Allied Health Sciences at Indiana University.

She returned to academics as the Director of Dialysis Services and Associate Director of the Nephrology Training program at the King/Drew Medical Center in Los Angeles. After receiving her M.B.A. from UCLA, she started her own clinical research company, Barnett Research & Communications, performing clinical trials for several international pharmaceutical companies. She has served on the Regional Quality Council and as a clinical researcher for Gambro Healthcare and is on the International Advisory Board of Shire Pharmaceutical Development Inc. Her interest in computer modeling lead to a certificate in clinical biomedical informatics from Stanford University and her current position at the RTRN DTCC.

Dr. Barnett is an Adjunct Associate Professor of Medicine at Charles R. Drew University and a specialist in Clinical Hypertension as designated by the American Society of Hypertension. She is also a Fellow in the American College of Physicians and was voted one of America's Top Physicians 2007 by the Consumers' Research Council of America.

Philip J. Baty, MD

Philip J. Baty is a Board Certified Family Physician who graduated in 1985 from the University of Notre Dame with a degree in Psychology and Wayne State University School of Medicine in 1989. He went through the Grand Rapids Family Medicine Residency Program (GRFMR) graduating as the chief resident in 1992. He immediately joined Family Care Physicians, P.C. He has remained a member of the P.C. as it has changed names to Advantage Health Physician Network (AHPN). While there he has taught and won awards from the GRFMR program in the areas of Diabetes management and Evidence Based Medicine (EBM). He has also been a member of the AHPN Quality Improvement Committee since joining the organization. Currently he chairs the Quality Improvement Committee. With his leadership Advantage Health Physician Network has been a leading quality provider in Priority Health HMO, Blue Care Network and Blue Cross Blue Shield of Michigan. In addition over 60 members of AHPN have obtained NCQA certification in Diabetes Care. He has worked with faculty members from Michigan State University School of Medicine and University of Michigan School of Medicine on projects as a member of the GRIN research network. These projects have taken known research ideas and applied them to real patients in primary care.

Francis D. Chesley, Jr., M.D.
Director, Office of Extramural Research, Education, and Priority Populations
Agency for Healthcare Research and Quality
540 Gaither Road, Room 2034
Rockville, MD 20850
office: (301) 427-1521

Christopher G. Chute, MD, DrPH

Dr. Chute received his undergraduate and medical training at Brown University, internal medicine residency at Dartmouth, and doctoral training in Epidemiology at Harvard. He is Board Certified in Internal Medicine, and a Fellow of the American College of Physicians, the American College of Epidemiology, and the American College of Medical Informatics. He became Head of the Section of Medical Information Resources at Mayo Foundation in 1988 and is now Professor and Chair of Biomedical Informatics. As a career scientist at Mayo, Dr. Chute's NIH funded research in medical concept representation, clinical information retrieval, and patient data repositories have been widely published. Dr. Chute directs Mayo Clinic's CTSA Biomedical Informatics Core, and serves on the Mayo Clinic Data Governance and the enterprise IT Oversight Committees. He is presently Chair of the US delegation to ISO TC215 for Health Informatics, Chair of the Biomedical Computing and Health Informatics study section at NIH, Chair of the Board of the HL7/FDA/NCI/CDISC BRIDG project, on the Board of the Clinical Data

Interchange Standards Consortium (CDISC), Secretary of the American College of Medical Informatics (ACMI), and Chairs the World Health Organization (WHO) ICD-11 Revision. He also serves on strategic advisory panels to NCRR and NHGRI within NIH. Recently held positions include the ANSI Health Information Standards Technology Panel (HITSP) Board member, Convener of Healthcare Concept Representation WG3 within the ISO Health Informatics Technical Committee (TC215), Co-chair of the HL7 Vocabulary Committee, Chair of the International Medical Informatics Association (IMIA) WG6 on Medical Concept Representation, American Medical Informatics Association (AMIA) Board member, and multiple other NIH biomedical informatics study sections as chair or member.

John Hickner, MD, MSc

John Hickner, MD, MSc, is Professor and Vice Chair of Family Medicine at The University of Chicago. Dr. Hickner came to The University of Chicago in September 2003 to develop a new Department of Family Medicine. He received his M.D. degree from Indiana University, completed his family medicine training at the Medical University of South Carolina in Charleston in 1978, and earned a Masters degree in clinical research design and biostatistics at the University Of Michigan School Of Public Health in 1995. From 1978 to 2000 Dr. Hickner practiced the full spectrum of rural family medicine, taught medical students and led a clinical research program at the Upper Peninsula Campus of Michigan State University. From 2000 to 2004 he was the founding director of the American Academy of Family Physicians (AAFP) National Research Network. During the past 25 years he has participated in more than 70 practice based research projects as principal investigator, co-investigator, data gatherer or study subject in three research networks which he helped to found. He is head of the practice based research unit of the University of Chicago CTSA program. Improving the quality and safety of primary care practice is his research area, with recent projects in pay for performance, access to care, and improving the safety of testing and medication management. He collaborates with Access Community Health Network and Chicago's South Side Health Collaborative. He is a founding member of the editorial board of The Journal of Patient Safety and a member of the steering committee of the Chicago Patient Safety Forum.

Loretta Jones, M.A.

Loretta Jones, M.A., is the founder and Executive Director of Healthy African American Families (HAAF) II. As a "Community Gatekeeper" Loretta Jones has dedicated her entire life towards the hope and healing of community and society-at-large. Her career as a civil rights activist, health policy advocate, and social architect has spanned more than 30 years. In an effort to level the playing field for all people, Ms. Jones continues her unyielding commitment as a change agent against disparities in human health, development, and opportunity. She is a co-investigator of the NIMH UCLA/RAND Center for Research on Quality in Managed Care, the NIA UCLA Center for Health Improvement in Minority Elderly (CHIME), and the NIH Drew/UCLA Project EXPORT, as well as a recipient of numerous CDC grants and contracts. She is a member of the UCLA Institutional Review Board (IRB) for protection of human subjects and on the National Children's Study-Los Angeles Ventura County Study Center (NCS-LAVSC) Committee. In addition, she is a Community Faculty member and on the 4-Year Medical School Planning Committee at Charles Drew University of Medicine and Science. She is also a member of the NIH National Institute of Child Health and Human Development (NICHD) Community Child Health Research Network (CCHN), and a member of the American Academy of Nursing Advisory Council. She was the lead author on an article published in The Journal of the American Medical Association (Jones L, Wells K, "Strategies for Academic and Clinician Engagement in Community Participatory Partnered Research." JAMA, January 24, 2007). She served as a Commissioner for the Joint Center Health Policy Institute's Dellums Commission (2005-2006) and was a Family and Youth Stakeholder Member for the National Center for Children in Poverty (NCCP) in 2005. In 2004, Ms. Jones was honored as the first recipient of the Centers for Disease Control and Prevention Award for National Contribution to Minority Health Programs, Research and Surveillance–Department of Reproductive Health. She also served as a member of the Advisory Council planning NICHD's longitudinal child health study and chaired its Social Justice committee. Loretta Jones currently resides in Los Angeles, California, the area she so tirelessly serves.

David Meyers, MD, FAAFP

David Meyers, MD, FAAFP recently was appointed the Director of the Center for Primary Care, Prevention, and Clinical Partnerships at AHRQ. Previously he helped to direct the Center's Practice Practice-Based Research Network initiatives, served as a medical officer with the U.S. Preventive Services Task Force and as a project officer for the Agency's Health IT portfolio. Before joining AHRQ in 2004, he practiced family medicine including maternity care in a community health center in southeast Washington, DC and directed the Georgetown University Department of Family Medicine's practice-based research network CAPRICORN. He is a graduate of the University of

Pennsylvania School of Medicine and the Providence Hospital/Georgetown University Family Practice Residency. After residency, he completed fellowship training in primary care health policy and research at the Georgetown University Department of Family Medicine.

Jonathan C. Silverstein, MD, MS

Jonathan C. Silverstein, Associate Director of the Computation Institute of the University of Chicago and Argonne National Laboratory is associate professor of Surgery, Radiology, and The College, scientific director of the Chicago Biomedical Consortium, and president of the HealthGrid.US Alliance. He focuses on the integration of advanced computing and communication technologies into biomedicine, particularly applying Grid computing, and on the design, implementation, and evaluation of high-performance collaboration environments for anatomic education and surgery. He holds an M.D. from Washington University (St. Louis) and an M.S. from Harvard School of Public Health. He is a Fellow of the American College of Surgeons and a Fellow of the American College of Medical Informatics.

Dr. Silverstein provides leadership in information technology initiatives intended to transform operations at the University of Chicago Medical Center and is informatics director for the University of Chicago's Clinical and Translational Science Award (CTSA) program (funded via the NIH National Center for Research Resources). He has served on various national advisory panels and currently serves on the Board of Scientific Counselors for the Lister Hill Center of the NIH National Library of Medicine.

Jon White, M.D.

Jon White, M.D., directs the Health Information Technology (Health IT) Portfolio at the Federal Agency for Healthcare Research and Quality (AHRQ). Dr. White is responsible for setting the programmatic direction of AHRQ's Health IT projects, and leads a team of diverse and talented individuals at the Agency. Dr. White has extensive experience developing and managing Federal grants and contracts programs. He has directly managed numerous projects on quality measurement and improvement, electronic prescribing, standards development, health information exchange, clinical decision support, and implementation of health IT in diverse settings around the country. He participates in several national initiatives to improve the quality of American healthcare.

A board-certified family physician, Dr. White received his Medical Degree from the University of Virginia and trained as a resident at Lancaster General Hospital in Pennsylvania, where he received the national AAFP Award for Excellence in Graduate Education. Prior to his tenure at AHRQ, he was chief medical information officer and associate residency director of Lancaster General Hospital.

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ROSTER OF PRINCIPAL INVESTIGATORS

Re-engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks (BAA-RM-04-23)

Dennis Confer, M.D.
Chief Medical Officer,
National Marrow Donor Program
3001 Broadway St NE, Suite 500
Minneapolis, MN 55413
Tel: (612) 362-3425
Fax: (612) 627-8125
E-mail: dconfer@nmdp.org
Contact: thousema@nmdp.org

Lee Green, M.D., M.P.H.
Professor and Associate Chair for
Information Management
University of Michigan Family Medicine Office
1018 Fuller Street - 120
PO Box 421
Ann Arbor, MI 48109-0723
Tel: (734) 998-7120
E-mail: greenla@umich.edu

Carol Dukes Hamilton, M.D.
Associate Professor of Medicine
Division of Infectious Diseases and
International Health
Department of Medicine
Duke University Medical Center
2400 Pratt Street, Room 0311
Durham, NC 27710
Tel: (919) 684-3279
Fax: (919) 681-7494
E-mail: dukes002@mc.duke.edu

Robert Harrington, M.D.
Professor of Medicine
Division of Cardiology/
Department of Medicine
Duke Clinical Research Institute
Box 3001
Durham, NC 27710
Tel: (919) 668-8749
Fax: (919) 668-7072
E-mail: harri019@mc.duke.edu

Stephen Johnson, Ph.D.
Associate Professor
Columbia University
Department of Biomedical Informatics
Vanderbilt Clinic VC5
622 W 168th St.
New York, NY 10032
Tel: (212) 305-1858
Fax: (212) 305-3302
E-mail: Stephen.Johnson@dbmi.columbia.edu

James Kahn, M.D.
Professor of Medicine
University of California, San Francisco
PHP Medical Informatics Group
510 Treat Avenue (Green Glen Annex)
San Francisco, CA 94110
Tel: (415) 476-40823 x108
Fax: (415) 514-8377
E-mail: jkahn@php.ucsf.edu

J. Richard Landis, Ph.D.
Professor, Biostatistics and Statistics
Director, Division of Biostatistics
Center for Clinical Epidemiology & Biostatistics
University of Pennsylvania School of Medicine
423 Guardian Drive
600 Blockley Hall
Philadelphia, PA 19104-6021
Tel: (215) 573-4922
Fax: (215) 573-4865
E-mail: jrlandis@cceb.upenn.edu

Eric Larson, M.D., M.P.H.
Director, Center for Health Studies
GroupHealth Cooperative
1730 Minor Avenue, Suite 1600
Seattle, WA 98101
Tel: (206) 287-2534
Fax: (206) 287-2871
E-mail: larson.e@ghc.org

Alan Morris, M.D.
Professor of Medicine
LDS Hospital
325 Eighth Avenue
Salt Lake City, Utah 84143
Phone: (801) 408-1610
Fax: (801) 408-1671
Email: amorris@ihc.com

Kevin Peterson, M.D.
Assistant Professor
Department of Family Practice and
Community Health
University of Minnesota
Box 381 UMHC
6-240 Phillips-Wangensteen Bldg.
Minneapolis, MN 55455
Tel: (612) 624-3116
Fax: (612) 624-3037
E-mail: peter223@umn.edu

Gregory Reaman, M.D.
Chair, Children's Oncology Group
National Childhood Cancer Foundation
440 East Huntington Drive, #300
Arcadia, CA 91006
Tel: (240) 235-2220
Fax: (301) 718-0047
E-mail: greaman@childrensoncologygroup.org

Robert Williams, M.D.
Department of Family and Community Medicine
MSC 09-5040
1 University of New Mexico
Albuquerque, NM 87131
Tel: (505) 272-2165
Fax: (505) 272-8045
E-mail: rlwillams@salud.unm.edu

Re-engineering the Clinical Research Enterprise: Inventory and Evaluation of Clinical Research Networks (RFP-NIH-NHLBI-RM-04-022)

Stephen Durako
Vice President, WESTAT
1650 Research Blvd.
Rockville, MD 20850
Tel: (301) 738-8300
Fax: (301) 294-2040
E-mail: SteveDurako@westat.com

Nancy L. Dianis, RN, MS
Vice President, Westat
1650 Research Blvd.
Rockville, MD 20850-3195
Tel. 301-294-2885
Fax. 301-738-8379
E-mail: Nancydianis@westat.com

Richard Haubrich, M.D.
Associate Professor of Medicine
Division of Infectious Diseases
Department of Medicine, 8208
University of California, San Diego
Antiviral Research Center
150 West Washington Street, Suite 100
San Diego, CA 92103
Telephone: (619) 543-8080
Fax: (619) 298-0177

CASE STUDY #1 – CLINICAL RESEARCH INFORMATICS AND INTEROPERABILITY

Group Members: **Lee Green, (MCRC)-Lead, Kevin Peterson (ePCRN), Dick Landis (CRN Harmony)**

Group Topics:

- **Standards**
- **Open Source**
- **Brokering**

Case Study #1: MCRC -
Principal Investigator: Lee Green

Technical Interoperability between Clinical and Research Systems in a Multi-Dimensionally Heterogeneous Environment

Interoperability is widely acknowledged to be a desirable goal for biomedical informatics. The US Federal government has mandated that most Americans must have access to an interoperable electronic health record by the year 2014.[1] Biomedical research faces many of the same interoperability barriers as clinical operations. A recent review of the needs and barriers facing clinical researchers with respect to data management recommended a focus on three components: standardized information models; ability to track provenance of data as they evolve over time; and service cores to facilitate the first two components, plus a spectrum of support options to meet the needs of researchers. The authors conclude: ‚ÄúThese basic infrastructure components could provide considerable secondary benefits, such as increased collaboration and greater leveraging of existing research personnel for core science roles.[2]

In fulfillment of an NIH Roadmap "Re-Engineering the Clinical Research Enterprise" Broad Agency Announcement contract[3], the University of Michigan implemented a hybrid clinical care/research network that interconnected a depression surveillance network, a cardiovascular research network, a practice-based research network (PBRN), and a clinical trial management system via an automated Honest Broker that routed data from one network to another securely and without compromising patient/research subject privacy.[4] Each of the computer application systems involved were created by different organizations, some commercial and some institutional; all ran on physically remote computer systems with heterogeneous operating systems, were written in different programming languages, and employed different terminologies for internal storage of clinical, demographic, and laboratory data; and all systems used their own opaque patient identifier scheme.

Communications between the various computer systems employed the standards-based Service- Oriented Architecture paradigm as a transport layer. Message data points were encoded, where possible, using either SNOMED-CT or LOINC as the standard. Message content was formatted into XML documents. In some cases, the document content was structured using the Health Level 7 Clinical Document Architecture standard; in others, a message schema published by the Honest Broker system was employed.

We learned a number of important lessons regarding interoperability from a technical perspective. First, the messaging transport and encoding technologies and accompanying development tools can be formidably complex, and a steep learning curve was faced by all

members of the technical teams. Second, standards-based data encoding systems use opaque identifiers that are independent of cultural milieu and local language. This greatly benefits machine readability and opens the door to eventual internationalization of the application and its messages, but it makes messages difficult for humans to read and understand when problems arise. Third, we found that programming tools interpreted even widely adopted international standards differently, eroding their usefulness in pursuit of interoperability.

While the technical aspects were challenging, the most significant obstacles we encountered were not technical but organizational: the creation and communication of a shared overarching vision; scope creep in terms of goals and desired features; siloization necessitated by pre-existing funding mechanisms and conflicting priorities; coordinating approval processes of multiple IRBs; and the well- documented difficulties involved in distance-based team building.[5] There were anxious moments as tactical quandaries were resolved on an aggressive project timeline, but the endeavor was ultimately successful, showing that even such "soft" barriers can be surmounted.

The demonstration showed us that decentralized research data processing is already possible, and can become more efficient over time through the creation of an arsenal of re-usable standards-based communication protocols, messages, and common data elements, and the nurturing of organizational processes and structures. As networked research projects and consortia become more common, data interchange conventions will become a ubiquitous feature of the translational research landscape. Once these are in place, research teams will be able to engage in projects of almost any complexity and scope. An initial investment from domain stakeholders will bear copious fruit in the nature and breadth of research that will be conducted under this new paradigm.

References

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[2] Anderson NR, Lee ES, Brockenbrough JS, Minie ME, Fuller S, Brinkley J, Tarczy-Hornoch P. "Issues in Biomedical Research Data Management and Analysis: Needs and Barriers." Journal of the American Medical Informatics Association 2007; 14: 478-88.

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Case Study #1 – AGNIS
Principal Investigator: Dennis Confer

AGNIS leadership team: Dennis Confer, Mary Horowitz, Doug Rizzo, Martin Maiers, Ken Bengtsson and Paul Zyla.

AGNIS (A Growable Network Information System) is an open-source project of the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR). The AGNIS project team, which is focused on hematopoietic cell transplantation (HCT) research, recognized at the outset the need for a comprehensive set of data elements that would be accepted and used by the HCT community. The National Cancer Institute had created a public repository for fully defined (ISO/IEC 11179 compliant) data elements. This repository, called the Cancer Data Standards Repository (caDSR), had been built with numerous advanced features including the ability to utilize object oriented data models defined by the industry-accepted Unified Modeling Language (UML). The AGNIS team developed a UML model that encompassed all components of the HCT process. The team conducted a series of meetings with an internationally constituted committee of physician researchers intended to reach consensus on the standardized set of HCT data elements. In defining these accepted data elements, attempts to introduce the UML model for HCT data were unsuccessful. In contrast to the compact UML representation, the users preferred forms-based representations for HCT data. Traditional forms, paper or electronic, were tied in the minds of users to time points on the HCT timeline. The timeline-based "model" was familiar and made sense to them. The AGNIS team elected to populate caDSR with accepted forms-based HCT data elements even though this dramatically increased the required caDSR curation effort. This experience illustrates the difficulty of introducing new technologies and concepts into an established field of research.

Case Study #1: TB Trials Network
Principal Investigator: Carol Dukes-Hamilton

We are living in a society with untapped uses of our cutting edge technology that not only have the potential to improve the health of our population, slow down the increase of healthcare costs but to also improve the quality of data used across health entities.

Addressing the costs of healthcare can have a significant downstream impact for other health entities by taking the data collected during a healthcare encounter and reusing it. Secondary uses of data is possible if it is standardized at an atomic level in a healthcare setting where it is originally collected then modeled to be used in electronic health records, decisions support systems and then shared to other groups such as surveillance, quality improvement and research.

Our case study has addressed that issue in a therapeutic specific environment. The standards team has assembled experts in the Tuberculosis and the standards community to design a methodology that has proven to be a complex challenge that produced 93 standard data elements for Pulmonary diagnosis and treatment which includes 300+ possible responses called permissible values. The data is modeled in class diagrams to show the relationship of the data points to each other and how they are classified in Tuberculosis activities. Working with the Healthcare Standards Development Organization HL7 and the Research Standards group CDISC we have linked data questions with

possible responses that are collected at the healthcare setting and can be reused in research. From this project we have produced a research example of how the data can be modeled in the SDTM CDISC standard for submission to the FDA.

This initial project accomplished a significant amount of ground in this therapeutic area in that 75-80% of the pulmonary TB environment is standardized with package #1. This standard will be reviewed by the research and healthcare communities to provide input on the consensus product that have been developed by the global stakeholders team.

An additional downstream use for this TB data and HL7 standards is to create a mechanism to share data with other NIH networks such as NIDA and DILIN for possible enrollment into their studies.

Case Study #1 – CTN
Principal Investigator: Robert Harrington

Topic: Standards

Clinical sites, particularly large healthcare systems and hospitals, have multiple disparate data systems in use to serve the needs of their clinical operations, and often, continuity with legacy systems. All of these same organizations also supply data to third parties, either as part of their operations (e.g. reimbursement requests) or to meet other organizational objectives (e.g. accreditation, performance metrics, public health reporting, and research). Typically this secondary reporting is accomplished by individual departments or research investigators developing their own ad hoc solutions to meet the particular reporting objectives. Often data is obtained or re-coded via retrospective chart review and reported by data entry into the 3rd parties system, recording on paper forms or at best, a customized electronic data exchange.

Very many efforts are underway to develop standards to leverage (and enable) the growing adoption of electronic health records and capability to exchange electronic data. Unfortunately these initiatives (even within a domain such as cardiovascular disease or within an organization such as the NIH) are proliferating, uncoordinated and often competing. Prior 'infrastructure' initiatives have tended to focus on national strategies to endorse specific products. Even well intentioned initiatives have their ability to learn from other initiatives and capacity for collaboration quickly saturated.

As part of the CTN Best Practices program a new initiative was formed to identify methodology that could be used across stakeholders and domains for the development of clinical domain-specific data standards. Through collaboration with the TB Trials Network and many external stakeholders, including CDISC and HL7 there now seems to be a growing consensus on methodology; however the ability to coordinate and leverage disparate initiatives continues. An outgrowth of the CTN Best Practices project was to develop a new entity hosted by HL7, the Clinical Interoperability Council, whose purpose is to provide experience, coordination and a forum for consensus on clinical content standards being developed internationally. The governance, stakeholder engagement strategy and agreed method to develop a master consensus set of clinical data elements is not yet worked out. Discussion on the development of a community-based organization (with linkages to Standards Development Organizations and other public and private efforts) to provide the coordinating mechanism for clinical content standards is welcomed.

Case Study #1 – Clinical Research Informatics and Interoperability

Case Study #1: InterTrial Project in the Clinical Trials Network at Columbia University Principal Investigator: Stephen Johnson

The concept of interoperability can be broadened to encompassthe exchange of information accurately, effectively and efficiently among individuals and organizations as well as information systems. Clinical research workflow in community practices and the systems and policies supporting offer numerous examples of problems with interoperability. Standards are lacking to 1)represent CR related data elements and activities, 2)determine structure of frequently used work-related forms and 3) represent the steps in a particular research process. The lack of interoperability of manual systemsinteroperability of computer-based systems extremely difficult.

We provide some examples for a fictitious clinical research coordinator, Sarah, to illustrate how lack of standards acts as a barrier to interoperability and leads to redundancy of work. Let us consider two activities that Sarah routinely performs as part of a clinical trial:completing Case Report Forms (CRFs), and completing a medication inventory and dispensation log. The two activities share overlapping data elements such as patient identifier, the number of the medication bottle, the date of dispensing, etc. The systems Sarah uses (mostly paper forms) to collect information for each activity are usually not standardized or integrated evenin the same trial. Sarah has to perform redundant data entry, copying the same values across two forms. Even when the CRF is completed online, the data are rarely reused for the medication inventory and dispensation log.The two forms may label the same data elements differently, compounded when forms undergo multiple revisions. Inconsistent, changing data elements present an enormous obstacle to interoperability in computer-based systems.

Sarah also discovers that she and the PI may have one interpretation for a field in a form, while the sponsor has another meaning in mind, and the representative of the clinical research monitoring organization yet another. Similarly, Sarah may have to submit two different forms for serious adverse event notification to different stakeholders. The forms contain the same information, but differ in terms of the lexical labeling of the data elements and structure. Also, other organizations may require the same form to be submitted in a different medium (a Fedex mail versus a fax) and at different durations (within 2 weeks, within 1 week etc). Each different form requires redundant work, increases confusion and raises the potential for error, which can be propagated into information systems.

Sarah also experiences many interactions between CR work and clinical practice. For example, a patient could be both a practice patient and a research study participant. This causes numerous transfers of information about laboratory values, medications etc between the clinical care side and the research side. For example, Sarah routinely needs to communicate any changes in a research participant's treatment to their primary care physician. Communicating across the boundary of CR and clinical care creates several obstacles through which information flows can be interrupted. In the sites observed we found almost no connection between information systems that support research (such as an EDC system) and clinical practice (eg EMR system).

Case Study# 1 – CNICS -
Principal Investigator: Jim Kahn

There were two functions that in this project. The first was how to obtain genotypic data and construct a database of these data elements. The first challenge is that there is no standard representation for genetic data. Genetic data is a string of numbers and letters. The number is constrained by the count of base pairs or amino acids coded from the base pair of a specific gene. The number is unique to each gene and to each life form. For instance the protease gene in HIV is different than a protease gene in a primate. There is a constrained number of letters associated with a specific number. There are 20 amino acids coded by 4 base pairs that combine in threes to identify the created amino acid. Base pairs are not usually recorded and so we did not need to record base pairs but we did need to record amino acids. We decided we could construct the base pairs in reverse. However the storage of amino acids was not standardized. We did not want to re-invent the process and amino acid storage information had been initiated by several groups including groups that had a proprietary interest in the databases. We turned to the NIH and mimicked the Los Alamos data base for genetic information since that had the greatest number of HIV sequences stored. What will be the definitive database remains unclear.

Case Study #1: CRN Harmony
Principal Investigator: J. Richard Landis

Integration of application frameworks and data standards should guide research data collection, so that data can be re-used in different contexts. The University of Pennsylvania (Penn), through the NIH Roadmap contract, implemented a standardized solution to informatics tools for conducting clinical research, as well as selected standards for data collection. Partnering with Oracle Corporation, the Penn's Roadmap project team utilized Oracle Pharmaceutical Applications (OPA) suite of tools to support the conduct of seven (7) clinical and translational research projects throughout the Penn School of Medicine. Oracle Clinical (OC) is a data collection and management tool that includes an object library structure containing re-usable study elements, such as common data elements (CDEs) and case report forms (CRFs).

In order to make this library applicable to many clinical studies, the Penn Roadmap team incorporated emerging standards from CDISC into new clinical study development. To begin, CDEs from the cancer data standards repository (caDSR) within the NCI caBIG global library were transfered to populate the Penn OC library. The team adopted a methodology incorporating the caBIG standards repository and tools for the identification of existing standard data elements contained in the caDSR when creating new CDE specifications. The Penn Roadmap project team identified seven clinical studies from four different departments to pilot CRF development, re-using CDEs from the OC global library, whenever possible. Progressively over time, as these CRFs were added to the global library of common data elements (CDEs), the number of CDEs and CRFs required to develop subsequent clinical trials in the same content area decreased considerably. Nearly 50% of all CRFs and CDEs developed as new in the first four studies were re-used from the global library in the remaining three studies. Consequently, the number of development hours needed to deploy OC data management systems within the same general content area, were reduced by nearly 50%.

Case Study #1 – Clinical Research Informatics and Interoperability

Utilizing the OPA suite of tools reduces the development effort and time required to produce a comprehensive, CFR part 11 compliant, data management system for a project from several months to as short as several weeks. Further efficiencies are gained through utilities that allow for the re-usability of database modules/structures for subsequent projects. We have begun assembling a CRF library, which was initially populated with a transfer of database elements from the NCI caBIG library. This library, and the CDEs contained within, can now be utilized to develop future clinical trials, and will be available to researchers throughout Penn Medicine.

Case Study #1: HMORN CCSN
Principal Investigator: Eric Larson

Coordinated Clinical Studies Network and the PRISM Project – Interoperability in the Broader Context of Interacting with Research Participants

Interoperability is often used to refer to the degree to which computer systems can share and use data from other systems (for example, different vendors' electronic medical records exchanging data). Thus, in some respects, interoperability is a means of transcending a "language barrier." As such, this concept could be broadly applied to other entities that interact in health care and research environments to assure that recipients of health-related messages truly understand what the sender is saying—medicine and medical research definitely have languages of their own. Part of our Coordinated Clinical Studies Network included a project called PRISM (Project to Review and Improve Study Materials) that embraces this expanded concept of interoperability.

Through the PRISM project, we determined that our consent forms and other study materials were typically written at grade levels much higher than our IRB-prescribed 8th grade target. By fielding materials written at advanced reading levels, were we compromising our ability to interoperate and communicate with potential study participants? Given the critical importance of clear communication in medical care, we extended this to the research context and created a suite of tools and training materials to encourage the development and use of materials that addressed the barrier of health literacy. The PRISM Readability Toolkit, an editing service for consent forms and other study materials, and training workshops comprise our suite of services.

We have disseminated the materials to a diverse array of constituents in health care and research from conferences for the health insurance community and public health departments, to the IRB community and health literacy researchers. Our PRISM "recipients" embody the fact that health literacy is indeed an issue that needs to be addressed via multiple avenues and stakeholders—it is a public health issue, a research issue, and a policy issue. To date, we have furnished the Toolkit to the National Heart, Lung and Blood Institute, the MD-Anderson Cancer Center, the Mayo Clinic, Kaiser Permanente and several other health care delivery systems, the Seattle-King County Department of Public Health, advocacy groups such as Patient Advocates in Research and the Research Advocacy Network, and more than two dozen academic institutions. Notably, PRISM was cited by the Joint Commission for the Accreditation of Healthcare Organizations as a uniquely accessible resource for tackling health literacy. Most recently, we presented PRISM at the Public Responsibility in Medicine and Research Conference (PRIMR) as a didactic workshop, with very strong positive feedback, including a suggestion that this session be repeated at subsequent conferences. Clearly, the need exists to reach patients where they

are and consider that the definition of interoperability needs to take more than technical machinations into account.

The PRISM Toolkit also served as a springboard to broader conversations in our local health care system, Group Health, which was seeking strategies to improve its patient health education resources on a wide scale. The CCSN PRISM team and representatives from across Group Health are now part of an organization-wide Plain Language Task Force which aims to improve our collective ability to communicate—and thus interoperate—with our patients about their health care experience.

Case Study #1 – Clinical Research in Critical Care
Principal Investigator: Alan Morris

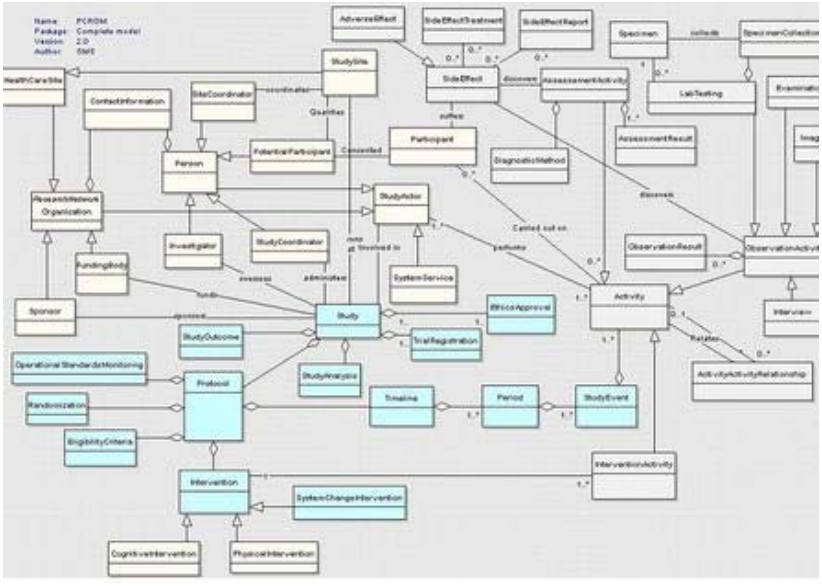
"Reengineering Clinical Research in Critical Care" Scenario

We used an adequately explicit computer protocol to achieve a replicable method for blood glucose control with intravenous insulin in multiple intensive care units in hospitals in different cultures. The computer protocol (eProtocol-insulin) enabled different intensive care units to perform in a replicable manner. eProtocol-insulin is driven by patient-specific input data and displays treatment recommendations intended to bring the patient's blood glucose within the 80-110 mg/dl target range.. This computer protocol enables the development of an extended research laboratory in which each clinical performance site replicates the behavior of other participating sites. Results form the interoperable clinical research method are thus more easily interpreted than are many clinical research results obtained with methods that vary significantly between institutions.

Case Study #1 – ePCRN
Principal Investigator: Kevin Peterson

PCROM Standard

The organization and management of clinical research differs substantially for research performed in networks of community-based primary care practices compared to other research settings such as tertiary academic centers. These differences in workflow, resources, and other organizational features must be accommodated by systems that support clinical research. To promote system interoperability, research models should incorporate the requirements of clinical research in community-based practices. The Primary Care Research Object Model (PCROM) represents an important and necessary link between the reference model of clinical research defined by BRIDG and the real-world design and implementation of



systems to support the design, execution, analysis and reporting of randomized clinical trials (RCTs) in primary care. The PCROM is a standard, computable representation in Universal Modeling Language (UML) of common use cases, activities, actors, and interactions required to complete an RCT in the complex environment of primary care. The model is organized into three interconnected sub-models: Trial Process, Trial Information Organizations, and People and Systems.

Case study

Prior to the development of the PCROM, every study independently created datasets based upon data elements provided by an investigator. Data elements were then entered into tables created by programmers, and provided with relational keys that satisfied the programmer or analyst. Unique elements essential to primary care often varied from study to study or were left out entirely. Data elements were not fitted to data collected in electronic health records or with data from similar clinical studies. The result was not only an inability to interoperate but sometimes an inability to even compare outcomes from similar studies. Development of electronic case report forms often required one to two months of programming work beyond completion of the study design.

The PCROM supplies a standard domain information framework for designing and evaluating research management systems and represents an important link between existing reference models and the real-world implementation of systems for managing practice-based primary care research. The PCROM provides developers with the specific functions and database structures required to manage research in primary care environments. It provides a "checklist" of requirements to assure that all fields necessary to manage research in a practice-based environment are included. The full functionality of the PCROM is seen when it is used in conjunction with standardized data structures such as the CaBIG DSR and EVS, as implemented in the ePCRN research portal. The ePCRN implementation of the PCROM promotes and guides the researcher in the use of standardized data elements, supports the reuse of previous questions and templates in new research designs, and improves comparisons of studies and subsequent meta-analysis. By allowing the researcher to electronically design a study based upon PCROM modeling, the role of the programmer is virtually eliminated. Database tables are automatically created from existing Java classes mapped to the UML model, and case report forms can be created by the computer within minutes of the completion of the study design. The PCROM is mapped to existing object models from HL7 for electronic health records, and from CDISC for clinical research, promoting true interoperability between these systems. Finally, the PCROM checklist provides an important evaluation tool for institutions in the process of purchasing a vendor-supplied clinical trial management systems intended for support of practice-based primary care research sites.

Case Study #1 – Clinical Trial Recruitment
Submitted by the ePCRN team - Principal Investigator: Kevin Peterson

In order to accelerate the translation of clinical research into practice, new partnerships with community medical providers who deliver the majority of care to the US population need to be developed. These partnerships should enhance the ability of investigators to conduct research, as well as facilitate delivery to clinicians of better tools to provide care. The electronic Primary Care Research Network (ePCRN) uses emerging technologies to implement open source solutions that expedite recruitment, facilitate research design, and

enhance performance of clinical research in community medical practices. In addition, the ePCRN solutions provide valuable clinical applications designed specifically for community clinicians including population-based chronic disease management tools, a multiple-disease registry, and enhanced communication tools. For patients, the ePCRN architecture provides substantially greater opportunity to participate in high quality research that has been screened and recommended to them by their primary care provider.

Case study

Recruiting for clinical trials has become increasingly difficult in traditional research centers. Although many potentially eligible patients may exist in a community, access to a medically defined population is often limited to appeals to the general public through newspaper, television, and radio advertisements. These may miss appropriate participants, appeal to the wrong populations, and be challenging to detail in nonmedical terms. Recruiting also often includes appeals to local medical providers. However in many medical practices research pamphlets and posters sent by researchers are discarded or ignored. Even informational visits by researchers to local clinicians are quickly forgotten in the midst of the competing demands of a busy community practice.

The ePCRN architecture substantially addresses these important issues. The researcher can now describe desired eligibility characteristics of a patient population in simple terms on the ePCRN website. The researcher is prompted with subconcepts and superconcepts to focus the description, and the final description imbedded into an electronic query using standardized codes from the Enterprise Vocabulary System (EVS) (CaBIG, NCI). The query is passed in a secure fashion to participating primary care practices from the Federation of Practice Based Research Networks, a national organization of over 2700 primary care clinics involved in clinical research. Participating clinics run the query automatically and return a count of potential eligibility. With permission of the regional FPBRN Director, providers are electronically notified of all patients in the practice eligible for the study. Any patient that the local physician identifies as appropriate is automatically contacted using email, text messaging, or a printed letter. Potentially eligible patients are provided with information about the study, can be referred to a website for more information, or be asked for permission to allow contact by the study investigator. The architecture incorporates a flexible multiple-disease registry based upon the Continuity of Care Record/Document (CCR/CCD) electronic health record (EHR) export standard and is supported by a wide variety of EHRs. This registry provides additional functionality for evaluating population-based performance measures, enhancing patient-specific clinical decision support, and promoting proactive engagement of patients by their local provider. The ePCRN architecture provides research directors, clinical research organizations, and clinical translational science centers with a sophisticated solution for easing recruitment burdens, increasing speed and success of clinical studies, and more successfully integrating primary care physicians and their practice populations into the clinical research enterprise.

Standards and open source tools that make this possible:

1. Standards: Integration of the Continuity of Care Record/Document (CCR/CCD) open standards architecture (ASTM/HL7); the National cancer Institute's Cancer Bioinformatics Grid (CaBIG) Enterprise Vocabulary System (EVS) and the CaBIG cancer Cancer Data structured Repository (CaDSR) to provide a standardized repository and the National Library of Medicine UMLS to provide a standardized ontology for coding and vocabulary; SOAP; LOINC, SNOMED, and RxNORM; the

Primary Care Research Object Model (PCROM) for primary care based activity diagrams and use cases to demonstrate how the software fits into a common work flow.

2. Open source: MySQL open source relational datasets; Globus toolkit; Internet 2/ Grid architecture; CaBIG toolkit; and standard programming languages.

Case Study #1 – COG-PBMTC
Principal Investigator: Greg Reaman

For the BAA-RM-04-23 project, the Pediatric Blood and Marrow Transplant Consortium (PBMTC) and the Children's Oncology Group (COG) developed a collaborative effort to enhance availability, safety and efficacy of pediatric BMT and to advance the science and application of BMT through coordinated development of research concepts and collection of data between the PBMTC, COG and related networks in BMT. Project participants in the COG and PBMTC participated in a series of teleconferences and meetings with participants from AGNIS to develop common data elements unique to transplantation, and data sharing and communication would ultimately occur between the PBMTC, CIBMTR and the BMT CTN (Bone Marrow Transplant Clinical Trials Network). There was concern that the PBMTC/COG activities would be duplicative of some of the AGNIS project goals and all participants expressed an interest in increasing efficiency by working together to achieve results and to help the BMT CTN incorporate a data translation plan to allow for better participation of PBMTC in BMT CTN trials. All collaborators agreed that working together on Common Data Elements was the place to begin joint efforts, which would allow the groups to define the shared data and then create a plan to move the data from one group to another.

Case Study #1- RIOS Net/PRIME Net
Principal Investigator: Robert Williams

Providing data collection and coordination function for a practice-based research network (PBRN) study operationalized across several collaborating PBRNs revealed that even the most basic data required attention to assure interoperability across networks. The information for which we most needed standardized models and time-sensitive tracking was basic member demographic data. PBRNs needed coordination on number and format for many of the basic demographic data elements – e.g., whether firstname/lastname are represented by one or two variables, whether email and postal addresses are both required, whether title/degree is required, and whether medical specialty is required. In addition, the problem of maintaining up-to-date lists of active network membership in these constantly changing individual networks proved to be an unanticipated challenge. It became clear that a database of active membership across a consortium with large numbers of clinician members requires constant scrutiny and updating. In addition, the coordinating center usually lacks access to the communication channels to keep the data current even when deficiencies are identified.

To address this problem we created a database with secured remote access that allowed for shared responsibility of data maintenance tasks. This system allowed coordinators at each individual network secured and authenticated access to the part of the collaboration's database that contained the list of individual network membership. In this manner, each of the collaborating networks could maintain their network's portion of the collaborative (while assuring privacy of other networks' members data). This tool was effective when used but

we discovered the degree of adoption and use of this tool varied considerably between individual networks. Even with the tool in place, these relatively fundamental data maintenance efforts proved to require a great deal of centralized service and support.

Designing software tools in a modular and repurposable manner allowed us to benefit from efficiencies across many different PBRN projects. For example, reusable CME administration software allowed for customized CME courses to be rapidly configured to support several different areas of research. Subject consent, pre- and post-testing, and automated follow-up contacts were all automated. Reusable, modular code also speeded the development and deployment of web-based survey instruments.

CASE STUDY #2 – INTEGRATIVE INFORMATICS IN SUPPORT OF TRANSLATIONAL RESEARCH

Group Members: Jim Kahn (CNICS)-Lead), Greg Reaman (COG), Dennis Confer (AGNIS)

Group Topics:

- **Lab data, organisms, tissues, cells, genes**
- **Balancing clinical & research needs**

Case Study #2 – MCRC
Principal Investigator: Lee Green

The MCRC's feasibility study integrated research subject recruitment and study management into the informatics environment of four different primary care practices. The MCRC infrastructure had to be integrated with several systems in each practice, most of which are legacy systems that are not designed to exchange information in standards-based ways, in order to make the process work.

The MCRC's feasibility study required that a universal registry and reminder system be implemented in the study practices, and used in their regular daily patient care and for QI activities. The practices used the system to accumulate coded, structured problem lists on patients, which they will transfer to the EHR they are now implementing. The system also delivers reminders for disease management, such as to insure that patients with diabetes have A1c measurements, and for preventive services, based on patient demographics and problem lists.

The reminder system was tied to the research support infrastructure, via a SOAP service. That part of the integration was under the study team's direct control, and while requiring significant effort was straightforward.

In each site, the reminder system had to be integrated with the site's scheduling system. The four sites had two different systems, one of which was capable of HL-7 messaging (v2.3) and the other of which required daily file dumps and FTP transfers to share its schedule data. The HL-7 messaging imposed an unplanned $7,000 on the project budget, while the file transfer method worked only because all the patients at those sites were pre-scheduled. (more to follow)

Two of the four sites were in an IT environment managed by a large vertically- and horizontally-integrated health system. In these sites, successful integration required close partnership with IT personnel who were very concerned about security issues. Study

laptops could not be used inside their firewall, so the clinics permitted study staff use of clinic computers. The non-standards-compliant browser used in the clinic system would not work with the research information system, so the clinic's IT staff installed a W3C-standards-compliant one for the project's use. The network in these sites was robust and stable, with abundant bandwidth.

The other two sites were clinics serving underserved populations, where finances were chronically tight. The networks were very limited in capabilities, and were unreliable, having been assembled in fits and starts by volunteers using available resources. The sites were connected by consumer-level DSL service, with dynamic IP addresses. Printer addresses changed whenever the routers were power-cycled, causing document print jobs to fail. The project overcame these difficulties with resources: leasing static IP addresses and commercial DSL service for the sites, and rebuilding their internal networks. The cost was surprisingly low, the effort was substantial, and the results successful.

Case Study #2 – AGNIS
Principal Investigator: Dennis Confer

AGNIS leadership team: Dennis Confer, Mary Horowitz, Doug Rizzo, Martin Maiers, Ken Bengtsson and Paul Zyla.

AGNIS (A Growable Network Information System) is an open-source project of the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR). It is a messaging system for automated exchange of clinical data describing experiences of individual hematopoietic cell transplant (HCT) recipients. How will AGNIS support translational research? NMDP maintains a repository of blood samples from nearly 50,000 individuals. In more than 15,000 instances, paired samples from a HCT donor and the donor's recipient are available. These samples are consented for use in research studies examining factors that influence HCT outcomes. Studies in progress are looking at the influence of HLA matching, the role of KIR (Killer cell Immunoglobulin-like Receptors), and impact of immune response modifier genes on transplant outcomes. The hypotheses in many of these studies are exploratory and successful completion depends upon large sample numbers and detailed HCT outcomes information. AGNIS facilitates such studies by easing the burden of outcomes data submission. Because of AGNIS, we expect to have more complete and timely data on HCT outcomes. Studies using repository samples will be more likely to identify genetic influences and create information that will alter clinical practice.

Case Study #2 – InterTrial Project in the Clinical Trials Network at Columbia Univ.
Principal Investigator: Stephen Johnson

Translational research encounters numerous challenges in the community practice setting that we observed. Research coordinators often have to engage in what is known as distributed cognition: work can only be carried out using multiple tools, including paper based artifacts (patient records, study binders etc.),telephone, email, fax, or computer software. Information exists in multiple places and is communicated over multiple channels. This environment is cognitively taxing, and can lead to poor and redundancy, delays and inaccuracies in work processes. A more integrated approach to information management could reduce these problems.

We consider examples involving Sarah, a fictitious clinical research coordinator. Every time Sarah needs to schedule a patient visit, she has to consult the protocol to determine the

next visit (time interval and window). She does this by looking at the visit scheduling chart that is provided with protocol documents and which she normally keeps fixed on wall for easy reference. Most trial participants are seen for clinical care in the same building but on a different floor, which complicates coordnation of study visits androutine clinical visits. She either calls the receptionist on the upper floor to determine the patients next regular clinic visit or she walks upstairs and checks the patient's medical chart to determine when he/.she is coming in next. She knows that if the trial visits are extrathe participants are less likely to come. Sarah then consults the patient to agree on the next visit date, keeping all the constraints in mind. Her main concern is to schedule the visit within the window allowed by the protocol. Things become more difficult when visits include an examination by the Principal Investigator (PI) in which case she also has to determine the PI's availability on the visit date. Once a visit date has been chosen, she makes a note in her appointment book. She records the patient's name, the time and date for the visit and the patient's telephone number, and gives a reminder card to the patient. One or two days before the scheduled visit Sarah will call the patient to remind him/her. Sarah uses several tools (such as the protocol visit chart, telephone, medical chart, verbal communication with participants, and an appointment book) to accomplish the activity.

The information needed to process the schedule resides in multiple locations and in multiple representations, leading to distributed cognition and highly fragmented workflow. An informatics solution must integrate several information resources and provide the necessary information management tools to manage CR related work. Our fieldwork suggests that an adequate information for this environment should possess the following features:

- be designed from the outsetto support collaboration among individuals that work in groups at a single site or across sites or organizations.
- empower end-users to collaboratively create and edit content (such as standard operating procedures), allowing them tobuild a shared knowledge base and information repository,customize features andextend the given system through simple mechanisms.
- protect the confidentiality of information through fine grained access control, authentication and other security mechanisms.
- become the preferred gateway for facilitating clinical research work by evolving into a platform that merges multiple information resources.

Case Study #2 –CNICS
Principal Investigator: Jim Kahn

There were two functions that in this project. The first was how to obtain genotypic data and construct a database of these data elements. That was described in Case Study #1. The second issue was how would we take this data and present it in different data bases for the clinicians? Here the display of information and the collecting and transferring the data became significant issues. The sites that we could collect this data were not initially secure. We had to educate them about security and data exchange. Next we had to determine how clinicians wanted data to be displayed. This was an iterative process and became clear that clinicians were used to looking at paper reports and wanted the same information presented as if it was a paper report. In addition the testing became more complex during this program. Initially only two enzymes were evaluated, reverse transcriptase and protease. During the program new data developed including envelope, CCR5 and CXCR4 receptors and new susceptibility testing focused on Replicative Capacity. We learned that keeping data up-to-date was complex. If we did not have flexibility to respond and include the new

data, clinicians would not trust our reports. A final change that occurred that we did not anticipate was the "versioning" of the different tests and the variance that each new version had. Not only did we have to keep data up-to-date with versions but we had to attach version logic to past collected data for clinicians to interpret the data.

Case Study #2 – CRN Harmony
Principal Investigator: J. Richard Landis, PhD

Increasingly, comprehensive and integrated applied informatics environments are being required by NIH to support large-scale clinical research projects. Applied informatics needs are appearing that exceed those associated with traditional Information Technology. We present a case study of one such situation.

In response to the NIH RFP No. NHLBI-HR-08-06 - Subpopulations and Intermediate Outcome Measure in COPD Study (Spiromics), a concentration of collaborative efforts from various Penn research groups, namely the Roadmap Program team, the CTSA informatics group, Penn IT support, the inter-disciplinary translational group, in collaboration with research groups from Children's Hospital of Philadelphia (CHOP) was required.

The Penn and CHOP response configured a Spiromics Genomics and Informatics Center (GIC) which required considerable scientific expertise in applied genomics, pathology, pulmonary medicine, epidemiology, biostatistics, genetics and proteomics, as well as informatics expertise in analysis of phenotypic and molecular data, operation of a biospecimen repository, development of bioinformatic resources, and development of a Controlled Vocabulary/ Ontology.

The Roadmap experience gained as a prelude to the CTSA provided tangible experience and results that were utilized as we proposed a Spiromics Clinical Research Network and GIC, clinical centers, core laboratories and radiology center. An extensive Specimen Repository for the Spiromics Clinical Research Network was organized that capitalized on the Pathology Department and Cancer Center development of a tumor and biosample repository to support Penn cancer researchers, included collaboration with NCI caBIG's tissue banking initative. Cooperation with the NCI's caBIG was a prominent feature of the Roadmap Programs. Spiromics was an opportunity to utilize Tumor Tissue Bank infrastructure and extend beyond cancer, thereby reducing Spiromics costs and taking advantage of experience in biosample banking.

In order to provide enhanced informatics resource, this research network will collaborate with the Biomedical Informatics in Translation (BIIT). BIIT is a Penn-CHOP CTSA initiative devoted to providing CTSA-Era informatics resources and services to investigators conducting clinical and translational research projects. The Biomedical Research Computing (BRC) organization will contribute to this network expertise in IT security, regulatory compliance, data storage, and data compilation across multiple, data generation facilities for analytical purposes.

We would not have considered our application to be competitive if it did not include both intensely applied informatics and the specialized IT required to support informatics. The Roadmap contract personnel formed the technical nucleus for both of these disciplines. Prior to the Penn Roadmap Program and formation of the CTSA BIIT from Roadmap personnel to support applied informatics and research IT, a credible response to this highly translational research-oriented RFP would not have been possible by Penn.

Case Study #2 – The CCSN and the Virtual Data Warehouse -
Principal Investigator: Eric Larson

The CCSN is comprised of 14 of the 15 research sites in the HMO Research Network, all of which are situated in health care delivery systems. Each delivery system, including Group Health in Seattle, Kaiser Permanente in 6 regions, and others across the U.S., operate independently as far as providing clinical care. However, the research scientists frequently collaborate on studies using the underlying data sources within each health plan. The challenge, then, was to devise a strategy for frequent extraction and aggregation of health plan data that was technically robust, facilitated compliance with IRB and HIPAA regulations, and accelerated the research process to the extent possible.

The Virtual Data Warehouse (VDW) had been conceived and launched prior to our CCSN contract. However, it was originally developed in support of cancer research projects for another research network, the CRN. The VDW maps legacy data to common structures (e.g. every site names the variable "date of birth" with the same name, "birth_date"), resulting in a federated database with multiple underlying data sources. This federated model maintains local control of the data, but still increases efficiency because a data extraction program can be written by a programmer at one site and sent to counterparts at the other Network sites, who can then run the extraction program with minimal modifications. Other advantages of this model are the ability to standardize methods and documentation, and avoid reinventing the wheel. We can also adapt common coding schemes as we build data structures—for example, tumor-related variables use NAACCR standards, pharmacy data uses NDC codes, etc.

Through the development of this federated virtual database, we've found that technology is clearly not the rate-limiting step. Data extraction programs can be developed and run in a matter of hours or at most, days. In our experience, the key areas for further exploration and problem-solving relate to other sociocultural and academic issues. How do we maximize the use of this warehouse now that it is created? We have built it—will they come? How do we entice collaborators to participate in multi-site data-only studies that may only address a single, focused question and thus preempt opportunities for multiple first-authored papers/ To leverage the full potential of these and other large-scale data resources, we need to remove these and other barriers to research, such as:

- iterative multi-site review processes
- site-specific (non-standard) data use agreements
- varying HIPAA interpretations
- intellectual property concerns
- amending tenure guidelines to ensure that scientific collaborators get "credit" for team-based publications

Another fundamental concern is the sustainability (and sustained quality) of an infrastructure resource such as this one, which was built with both research project funding, and sweat equity. The VDW has evolved over time and now contains a dozen different data structures, with others "under construction." As this is a resource designed for use by hundreds of investigators, any of whom may identify the need for a new data structure at any point in time, what is the most effective and efficient means of stewarding this resource, curating the data, and keeping the end-users apprised of its ongoing evolution.

Case Study #2 – Integrative Informatics in Support of Translational Research

Case Study #2 – Clinical Research in Critical Care
Principal Investigator: Alan Morris

"Reengineering Clinical Research in Critical Care" Scenario

We used an adequately explicit computer protocol (eProtocol-insulin) to translate research results to clinical practice. The computer protocol (eProtocol-insulin) enabled different intensive care units to deliver usual clinical care in a replicable manner close to that achieved in the developmental research unit (LDSH eProtocol). eProtocol-insulin is driven by patient-specific input data and displays treatment recommendations intended to bring the patient's blood glucose within the 80-110 mg/dl target range.. This computer protocol enabled 7 usual care hospitals to replicate the behavior of the research site (LDS eProtocol). eProtocol-insulin enabled translation of research results to usual clinical practice by exporting the computer protocol method to clinical practice sites.

Case Study #2 – Integrative Informatics in Support of Translational Research
Balancing clinical & research needs
Submitted by the ePCRN team - Principal Investigator: Kevin Peterson

The electronic Primary Care Research Network (ePCRN) uses emerging technologies to implement open source solutions that diminish, but do not eliminate, the burden of clinical research on the primary care practice. The ePCRN presents to primary care practices a simple business model that justifies participation in practical clinical research. The ePCRN integrates regional research offices that provide onsite support to the clinical practice. The model provides practices with electronic tools that enhance clinical delivery in exchange for enhanced research potential.

Case study

Although many patients may exist in a community who are potentially eligible and willing to participate in clinical research studies, access to medically defined community populations is often limited to appeals to the general public. Although some community providers are eager to participate in interesting research, as providers increasingly struggle to meet the demands of patients who are themselves battling within a complex health care system, the performance of research can place unintentional but substantial additional burdens on the local clinical team. As research burdens increase, providers are more likely to discard pamphlets and posters promoting research recruitment and participation. Even informational visits by researchers are quickly forgotten in the midst of the competing demands of a busy community practice. However, the limitation of research methodologies to simple designs that can currently be accomplished in primary care practices can compromise data quality, resulting in the disillusionment of researchers and further diminishing the potential for partnership. Previously, primary care practices have had little to gain from participation in research. Although sometimes providers were reimbursed, the reimbursement rarely compared well to potential clinical revenue for the same time. For clinical staff, research meant additional work sorting and completing forms that were not in their job description and were rarely reimbursed. For clinic administration research basically meant lost revenue. With the ePCRN model, installation of ePCRN software provides a flexible multiple-disease registry based upon the Continuity of Care Record/Document (CCR/CCD) electronic health record (EHR) export standard supported by a wide variety of EHRs. This registry provides additional clinical functionality for evaluating population-based performance measures, enhancing patient-specific clinical decision support, and promoting

proactive engagement of patients by their local provider. It facilitates identification of eligible subjects from a regional support unit, and provides electronic methods of contacting and consenting patients for contact with the researcher.

Case Study #2 – COG-PBMTC
Principal Investigator: Greg Reaman

For the COG-PBMTC collaboration, common data elements were originally planned to be developed in conjunction with AGNIS and the transplant community. Once data elements were defined, data capture tools and translation capabilities created, COG moved forward with development and activation of three PBMTC clinical trials using transplant-focused Group Data Elements (GDEs) that would become part of the common data element vocabulary at the National Cancer Institute. ASCT0431/ONC051: A Randomized Trial of Sirolimus-Based Graft versus Host Disease (GVHD) Prophylaxis after Hematopoietic Stem Cell Transplantation (HSCT) in Relapsed Acute Lymphoblastic Leukemia (ALL) was activated in March 2007 and involves a phase III clinical trial test of whether sirolimus has antileukemic in addition to immunosuppressive effects following allogeneic transplant. Minimal residual disease, mTOR pathway analysis, and immune biomarkers are all correlative studies integral to the clinical trial. The transplant data elements developed for this study and the other two trials (ASCT0521/SUP051 and ASCT0631/SCT051) resulting from the COG-PBMTC collaboration are now widely in use in transplant trials. Web-based, trial-specific educational tools were developed to ensure safe trial execution across a large number of centers who will be enrolling relatively small numbers of subjects.

Case Study #2 – RIOS Net/PRIME Net
Principal Investigator: Robert Williams

The PRIME Net Acanthosis Nigricans project provided an example of some of the “low tech” practical challenges that can occur when applying IT solutions across multiple diverse clinical environments. This project included collection of study-specific, patient-based data by individual clinicians at multiple sites in four different networks. Clinicians entered data in dedicated PDAs and the data were transmitted through web synchronization to a central server. Research assistants (RAs) at each study site were responsible for keeping the PDAs charged and synchronized prior to the start of the study. Based on past experience, we were aware that local firewalls would often block the synchronization process unless specially modified, and that installation of synchonization software on local PCs was burdensome for clinicians or clinic staff in addition to occasionally being suspect by local IT personnel. Hence, we planned a process wherein the RA would collect the devices at the close of a week’s data collection and handle all the synchronization operations on a study PC (not on any of the PCs available at the clinical sites). This centralization of the synching function was much more effective where used. However, limited RA availability at a second site led to those clinicians being “turned loose” to submit collected data on their own. As a result a few were unsuccessful, and hard-won data was never submitted due lack of onsite technical support. At a third site, several unexpected issues arose with respect to the RAs’ role in preparing and maintaining the devices. A critical protocol step of pre-study synchronization was omitted, with the result that early development versions of the forms were not replaced by final versions. In a few cases this led to irretrievable data loss, or, less grievously, data directed to unexpected final locations. In addition, charging instructions were often not followed, leading to incorrect timestamps which greatly complicate data reconciliation. Loss rates of mobile devices were also higher than expected, with theft of

multiple units occurring at two locations during the pre-study phase. Finally, one of the participating networks elected to substitute paper forms for the PDA because the paper better harmonized with clinical workflow in their practices. This was an expected but challenging variation, and while the PDA method offers advantages of enforceable data completeness, data standardization, and secure transmission, continuing cooperation from our clinical partners dictated that we be flexible with respect to the paper alternative.

CASE STUDY #3 – REDUCING BARRIERS TO RESEARCH

Group Members: Stephen Johnson (InterTrial)-Lead, Carol Dukes-Hamilton (TB Trials), Alan Morris (CCDS), Stephen Durako (IECRN)

Group Topics:

- **Regulatory Issues**
- **Workflow**
- **Human Performance**

Case Study #3 – MCRC
Principal Investigator: Lee Green

Any security-focused IT initiative has its share of technical barriers, and this project was no exception, but perhaps the most significant barrier to be overcome was more administrative than technical: coordinating a host of participants who were decentralized and physically disparate. The final data transfer solution was achieved though the collaborative efforts of five separate units spanning two health organizations. Two of the four involved primary care clinics and one of the three cardiac catheterization sites were part of a large multisite private integrated health system (which we will call Health System A) with its own information services department. At the University of Michigan, participating units included the Department of Family Medicine, the Michigan Institute for Clinical Health and Research (MICHR), Medical Center Information Technology (MCIT), and Medical School Information Services (MSIS).

MCIT worked closely with System A's IS department in order to erect a dedicated and persistent IPSec VPN tunnel between the University of Michigan Health System and Health System A's networks. This foundational element allows the networks to communicate in a trusted way without fear of external interference. MICHR and MSIS then layered on a dually-authenticated SSL mechanism to orchestrate specific trust between theClinfoTracker/Cielo Clinic and Honest Broker applications. Encrypted data exchange between the applications only occurs when each application is satisfied that (1) the identity of the other has been certified authentic by a common authority and (2) the IP address of the other has been checked against a list of known and trusted network locations. With secure communications now established comprehensively, Family Medicine, System A, MICHR, and MSIS combined forces to bring the ClinfoTracker and Honest Broker applications on-line and ready for use.

At the other two primary care sites and the other two catheterization sites, there was no virtual or physical private network. There we chose to use dually authenticated SSL via HTTPS over the public Internet for peer-to-peer (machine-to-machine) communication. With dual-SSL, we were able to both encrypt the information being transmitted using 128-bit keys as well as simultaneously authenticate both client and server systems using a public key infrastructure (PKI).

We unfortunately encountered several hurdles while configuring dual-SSL authentication between the Honest Broker and Cielo Clinic instances in two field sites. The first issue involved obtaining static IP addresses for the field systems, so that data could be reliably routed to them from the Honest Broker. This was accomplished through an arrangement with the sites' ISP. We next encountered an issue with our initial PKI arrangement. Our original security design involved leveraging the University of Michigan Certificate Authority (UM CA) to sign all SSL certificates. However, we discovered that their policies restrict them from signing certificates for non-UM owned systems, and therefore they were unable to sign the field sites' certificates. To circumvent this restriction and to allow for additional security, we created our own CA using OpenSSL, which we used to sign the certificates from both systems. With our own CA, we're able to restrict communication to those systems that have SSL certificates signed by our CA.

Our final hurdle was configuring both Cielo and Honest Broker, as well as a third test system using Apache HTTPD Server, to handle dual-SSL authentication. During the development and deployment of the communication components of the Honest Broker, and Cielo Clinic, we found that dual-SSL authentication was not well supported or documented in Java and Python. We therefore needed to develop custom components for both systems to fully support the communication and certificate handling upon existing OpenSSL and Java Secure Socket Extension (JSSE) libraries.

Case Study #3 – AGNIS
Principal Investigator: Dennis Confer

AGNIS leadership team: Dennis Confer, Mary Horowitz, Doug Rizzo, Martin Maiers, Ken Bengtsson and Paul Zyla.

The AGNIS project has propelled a cascade of events that will significantly reduce barriers to research. AGNIS (A Growable Network Information System) was conceived as a messaging system for automated exchange of clinical data describing experiences of individual hematopoietic cell transplant (HCT) recipients. The AGNIS proposal, prepared in response to the Roadmap RFP, was the product of two frequent collaborators, the National Marrow Donor Program (NMDP) and the International Bone Marrow Transplant Registry (IBMTR). Both organizations were actively engaged in collecting data and conducting research on HCT transplant outcomes; IBMTR collected voluntary data on all types of HCT procedures, while NMDP collected mandatory data focused only on unrelated donor transplantation. For the AGNIS proposal, NMDP brought IT and bioinformatics expertise to the project, while IBMTR lent its highly developed, international research collaborations. During the proposal preparation, it became clear that the two organizations needed to build closer collaborations and develop a single set of data collection forms. We agreed in early 2004 to combine our research data forms, containing several thousand similar and sometimes identical data elements, into a single set of harmonized research forms. This effort alone would reduce the data management burden for HCT research teams. But, within six months of beginning this effort, the two organizations elected to merge their research programs completely into a new research affiliation. To preserve 30 years of "IBMTR brand recognition" within the HCT community, the new operation was named the Center for International Blood and Marrow Transplant Research (CIBMTR) and began operations in July 2004. The AGNIS contract was awarded in October 2004 and became the collaborative effort of NMDP and the new CIBMTR.

Case Study #3 – Reducing Barriers to Research

During the first year of AGNIS funding, NMDP and CIBMTR continued the forms harmonization effort, but this was distinct and separate from AGNIS. The AGNIS team met with an internationally constituted advisory committee to discuss approaches to the "ideal" HCT dataset. At the same time the AGNIS technical team was examining a variety of available architectures in search of a suitable technical platform. This examination led the technical team to the NCI caBIG (cancer Bioinformatics Grid), and associated components in the caDSR (cancer Data Standards Repository) and EVS (Enterprise Vocabulary Services). A defining moment for AGNIS came with the decision to adopt software components of caBIG for AGNIS development and to use caDSR and EVS for definition and dissemination of common data elements (CDE). caDSR, as a public source of downloadable, reusable CDE, is expected to drive the HCT community toward common definitions and standardized data collection practices.

Another watershed event occurred December 2005 with passage of the Stem Cell Therapeutic and Research Act. The Act established a national outcomes database, the Stem Cell Therapeutic Outcomes Database (SCTOD), and mandated submission of data from every allogeneic HCT with a recipient or a donor in the U.S. An RFP seeking an SCTOD contractor was released by the Health Resources and Services Administration that further required the contractor to reduce the data submission burden for transplant teams and offer an electronic data capture (EDC) system. Armed with the nascent AGNIS system and an NMDP-developed EDC (FormsNet™), CIBMTR responded to the RFP and won the contract with a subcontract to NMDP.

The new harmonized research forms, however, far exceeded the data requirements of the SCTOD, so an initiative was started to indentify a suitable data subset, termed "Transplant Essential Data" (TED). For this initiative, CIBMTR convened another international team that included representatives from the European Group for Blood and Marrow Transplantation, Eurocord (the European cord blood transplant registry), and the Asia Pacific Blood and Marrow Transplant Group. Several conference calls and two in-person meetings were held in late 2006 and early 2007. The result was a new TED dataset, which all agreed represented the internationally accepted minimal dataset for evaluation of HCT activity and outcomes. Each participating organization has adopted the TED dataset. This dataset was also submitted to the U.S. Office of Management and Budget and accepted as the official SCTOD dataset in late 2007.

In December 2007, CIBMTR launched FormsNet 2.0, a completely redesigned EDC with capabilities to assign unique patient IDs, collect TED forms data and collect the new harmonized, comprehensive research form. A weighted randomization algorithm identifies recipient cases targeted for completion of the comprehensive research forms. Federally mandated SCTOD data must be collected on all allogeneic transplants, but patients may also consent for the use of these data, or the comprehensive data, in research analyses. A CIBMTR protocol for data collection and research has so far been approved by IRBs at 81 transplant centers.

AGNIS version 1.1.1 was released for free download in November 2007 (www.agnis.net). Full functionality of AGNIS has been delayed pending completion of CDE "curation" in the caDSR. But AGNIS will be the communication link between the FormsNet databases in Minneapolis and the SCTOD/research databases in Milwaukee. Several transplant centers and one U.S. commercial vendor (BMTSoft) are already incorporating AGNIS into their data management systems to facilitate streamlined, automated data exchange. A data exchange

agreement with Eurocord, which will utilize AGNIS, has also been signed, and an AGNIS interchange with EBMT is under development.

In January 2008, CIBMTR, NMDP and the American Society for Blood and Marrow Transplantation (ASBMT) co-sponsored an IT Summit to discuss the dramatic changes that have occurred and are continuing. One-hundred-forty IT and data management personnel from U.S. and international transplant centers attended the one and one-half day meeting in Minneapolis. In post-meeting surveys, overall content of the Summit was rated 4.4 on a five-point scale (with 5 as the highest rating). Ninety-five percent of respondents indicated that they would suggest IT program enhancements at their facilities. Asked if the meeting should be repeated, 99% said "Yes". Finally, respondents asked that CIBMTR, NMDP and ASBMT continue developing AGNIS, FormsNet and the tools for streamlined data management and reduced barriers to research.

Case Study #3 – TB Trials Network
Principal Investigator: Carol-Dukes Hamilton

In an effort to identify and address barriers to conducting clinical research in public health departments, Research Triangle Institute (RTI) in collaboration with Dr. Carol Dukes Hamilton's Roadmap project, set out to identify barriers, implement strategies to reducing those barriers and measuring the effects over a twelve month period of enrollment in a clinical trial.

RTI conducted site visits and gathered impressions from 95 clinical research personnel at Tuberculosis Trials Consortium (TBTC) recruiting sites including: 8 PIs 12 Study coordinators, 48 public health nurses and 27 clinical leaders (e.g. site directors or physicians).

Data analysis was conducted and aggregate interview notes were complied into specific matrices summarizing information. We then developed tables for recommendations via an overall matrix of ideas and recommendations.

Recommendations were shared and interventions were initiated at sites. From December 2006 to December 2007 data were collected from those sites. Study coordinators and site staff were interviewed each month to assess activities that occurred in the preceding month.

Interim findings (after 6 months of interviewing sites) are presented for three main domains: training, communication, and study visibility. Final analysis is near complete and will be shared in various forums in May 2008.

Case Study 3 – Clinical Trials Networks Best Practices (CTNBP)
Principal Investigator: Robert Harrington

CTN Best Practices (CTNBP) began in 2004 as a network of 38 U.S. hospitals specializing in cardiovascular research. Since that time, it has expanded to include several separate networks spanning research areas such as adolescent psychiatry, oncology, reproductive medicine, tuberculosis, and integrative medicine. What we have found to be universal to all therapeutic areas is the need for easy to access, comprehensive, training for site personnel involved in research. Because of this, one of CTNBP's specific aims is to implement programs and tools focused on building site capability, thereby enhancing recruitment, retention, and performance of clinical research sites and ultimately reducing barriers to research.

Case Study #3 – Reducing Barriers to Research

To help in our efforts, CTNBP created a Study Coordinator Advisory Committee (SCAC). The SCAC consists of 10 research coordinators representing 9 clinical sites. The SCAC identified a major challenge to clinical sites is that sites spend too much time and money seeking resources—such as training and templates—essential to conducting research. These resources either are just not available or are located in various places. These resources often are not advertised well. For clinical sites new to research, especially, finding and funding adequate resources is often prohibitive.

Our hypothesis was that a public Web site for sharing clinical research best practices, tools, and training can streamline clinical research practices by removing obstacles to relevant, high-quality clinical research; assist in standardizing research practices; and foster a collaborative multi-network of clinical research professionals, sites, and organizations. From this came the creation of the CTN Best Practices Web site (www.ctnbestpractices.org).

In January 2006, CTNBP opened the Web site to the public. Visits to the site have increased from 246 in January 2006 to a current steady status of 10,000+ hits per month. The Web site's most popular content is online training for clinical site personnel who do not have the time or budget to travel for training. Training topics include a clinical research overview, building a successful research site, Good Clinical Practice, and human research subject protection. To date, 1,500 online evaluations of our Web site training programs have been submitted, and we estimate that less than 20% of trainees complete an evaluation.

In conclusion, although the information that has been developed and collected and is now provided publicly on the CTNBP Web site is not novel, its organization and location in one easily accessible location is novel indeed. Approved resources posted on the Web site are being used by clinical research sites to enhance their performance and increase their participation in clinical research. Long-term outcomes continue to be evaluated through the use of an online feedback tool located on the Web site.

Case Study #3 – InterTrial Project in the Clinical Trials Network at Columbia Univ Principal Investigator: Stephen Johnson

Lack of proper tools to conduct research.Studies of workflow in community practice setting revealed that the lack of well designed tools to support clinical research coordinators introduced significant barriers to research efficiency.Paper-based binders and traditional methods of managing information often failed tosupport a collaborative working environment and required redundant effort. Existing computer system were often limited to EDC or basic scheduling and brought their own design flaws. A typical example is enforced expiration of computer passwords. Many CR software systems require passwords to be changed periodically, eg after 60 days. However, a coordinator may only use the system every 90 days, by which time her password has expired. She then has to go through a laborious process of getting a new one, e.g., from the sponsor's customer service. Moreover, we found that coordinators were frustrated by their lack of control over the organization of software and its features. Some of these barriers might be reduced through the introduction of new software systems developed with greater sensitivity to user needs and workflow, and could benefit from drawing on evidence from field studies.

Lack of adequate training. Field studies showed that lack of appropriate training orprior experience with keyoperations could present barriers to clinical research performance. While coordinators often receive training in general research competencies (eg. regulatory issues), there is often no explicit guidance in navigating the complex array of people, tools

and computer systems used within a particular work setting. It is a tacit assumption that individuals will acquire these skills through the normal course of their work. Software systems provide a prime example of these tacit assumptions. Field studies showed thatmany coordinators lack sufficent knowledge for operating computer software, and have low self efficacy for learning new technologies and applying them in their work. This can lead to inefficiency in research activities and the potential for error. Some of these barriers could be reduced by making tacit research processes more explicit and formalized. In particular, it should not be assumed that software will be used effectively merely because it is present. Information systems should be introduced with appropriate training initiatives designed to promote effective usage. Workflow studies can provide insight into research activities that require improved formalized and training.

Conflicts in organizational goals. Many of the clinical research coordinators interviewed in our study reported that research was perceived as a low priority and characterized as an "orphan" activity in the organization. A typicala site might have only a single investigator engagingin research, while the remainder of the clinicians in the practice are focused on patient care. This often leads to parallel cultures in a single site, with various activities poorly integrated. An example of this can be seen in the role of research coordinators. Because the practice is not primarily designed to perform research activities, it is difficult to distribute tasks across site staff and maintain continuity and quality. Instead, the usual solution is to have the coordinator perform virtually all activities related to clinical research. However, the coordinator may also have to occasionally perform patient care tasks, or even administrative tasks(e.g. answering phones). Some of these barriers could be reduced by reviewing and possibly re-engineering the organizational structure of practices engaged in research. A more integrated mission that integrates research and care could help reduce competition for limited resources. Restructuring of roles and responsibilities could help distribute work more equitably and efficiently. Worflow analysis could be used as a tool to report back to providers and administrators and provide suggestions for alternative organization.

Case Study #3 – CNICS
Principal Investigator: Jim Kahn

The project had two major elements genotypic data for HIV and phenotypic data of HIV. The genotypic data was mostly carried out in research labs that each site had control over. The phenotypic data was done centrally by a commercial entity with little to gain and afraid that it had much to lose by providing this data. Anticipating problems, the contract application included a letter of support from the commercial entities stating their support for the project. In the end their intellectual property was felt to take precedence and they did not want to provide the data. What ensued was almost a 4 year odyssey of determining how to protect the IP rights for the commercial entity and the IP rights of investigators. In the end this work was done and contracts were signed between the entity and the CNICS sites. However there were significant delays and obstacles. How were the obstacles removed? We suggested that unless they changed their opinion we, as a group, would no longer use their commercial product but would change to a competitor. The competitor had a small amount of the market share but that would grow if all 8 sites moved at once.

Case Study #3 – Reducing Barriers to Research

Case Study #3 – CRN Harmony
Principal Investigator: J.R. Landis

The NIH Roadmap program seeks to improve the links between science and technology by fostering research collaboration across sectors. In particular, research collaboration between university and industry. This case study will focus on the barriers encountered in the collaborative efforts of a major university data coordinating center and a leading, worldwide information technology industry.

The goal of this collaborative partnership was to expand the use of clinical research informatics by converting and integrating sophisticated data management systems tools utilized by the pharmaceutical industry to an academic medical center suite of tools for use in NIH sponsored clinical trials. Partnering with Oracle Corporation, the University's Roadmap project team evaluated the functionality of the Oracle's Pharmaceutical Applications (OPA) suite of tools to determine the modifications required to effectively execute the tools in a randomized clinical trial.

The initial focus of this project was on the re-engineering of the Oracle pharmaceutical adverse event reporting system application (AERS) for use in academic medical center (AMC) clinical trials conducted in an NIH funded urology research network. Whenever a project involves implementing packaged software or new hardware, knowledge transfer from vendor/consultant to the project team is critical. The industry consultant and university project team held intensive meetings to evaluate the dominant design of the application and identify the differences in sequential steps needed and differences in process flow. There is a significant difference between the work flow of the pharmaceutical centralized (or "in–house") model and the distributed (or "site initiated") model for which we were attempting to modify the system to accommodate.

The first step was defining "user roles", for example, research coordinator, principal investigator, data entry and data coordinating center. Each of these respective users has a defined set of responsibilities and permissions with regard to entering or confirming information for an event within AERS. When a user logs onto the system, they are directed to their mailbox which lists all of the current cases and various status indicators. The next step was to review the existing data screens to determine relevant data fields. Some aspects of adverse event reporting in the academic clinical environment i.e. product complaints, do not merit the level of rigor required in the pharmaceutical industry.

One of the most valuable features in AERS is the ability to auto populate many of the fields with data previously entered in the clinical trials database such as past medical history, concomitant meds, past lab results. This historical information in combination with event facts and links to reference information like the product repository allows the Principal Investigator to make the most informed decisions when assessing an adverse event. We evaluated the issues of work flow. We wanted research coordinators and site staff to be able to enter objective data regarding an event and have that data available for either programmatic or manual review at the data coordinating center (DCC). The type of review would be contingent on the type of event, i.e., expected adverse event, unexpected serious adverse event, etc. and the defined reporting requirements (24 hour, 5 days, etc.) The Principal Investigator would receive the event information simultaneously with the DCC and would be able to make their assessment regarding relatedness, grade, and action, if

necessary. Each user has the ability to update or add data respective to their user privileges at any point in the process.

Custom or standard reports, such as a MedWatch report, can be automatically generated by any of the users, according to assigned user role. AERS has the ability to auto generate a complete narrative based on the information entered for a specific event. A "submission wizard" will guide the user regarding pre-programmed reporting requirements and track submission status.

The goal of expanding research informatics in this instance was not achieved. Though our initial pilot testing of the AERS system demonstrated that this specialized application could be re-configured for use in AMC clinical research, several barriers, both technical and organizational prevented the full implementation of the AERS system beyond a pilot testing phase for use in a large scale clinical trial. These barriers were identified in the following areas:

Academic medical center adverse reporting processes

- Written materials for adverse event reporting in academic medical center's focus on communicating responsibilities to individual investigators. 'Details' rely on investigator discretion; this approach encourages tremendous variability in processes and quality of adverse event reporting.
- There are no set standards for the overall event reporting process in the academic environment, to promote consistently high quality adverse event reporting.
- Current academic medical center supporting informatics infrastructure is not designed to facilitate systematic management of the adverse event reporting processes.

Re-engineering AERS application and seeking institutional support for clinical research informatics

- Partnering with a large corporation to negotiate re-engineering of a commercial product requires concerted resources, effort, communication and coordination for AMCs. At most universities, this process is typically fragmented and occurs across different AMC offices.
- Re-focus current AMC perspective in recognizing that the benefits of a institution-wide infrastructure to support adverse event reporting processes is an organizational imperative and not solely the responsibility of the clinical investigators.

Our AERS re-engineering activities in relation to the identified barriers requires further investigation. It is clear that the level of resources required for adapting AERS modifications was largely underestimated and plays a key role in the transition of this tool from industry research to academic research.

Case Study #3 – Reducing Barriers to Research

Case Study #3 – The Coordinated Clinical Studies Network (CCSN) - Alternative Approaches to IRB Review
Principal Investigator: Eric Larson

The Coordinated Clinical Studies Network (CCSN) is comprised of sites in the HMO Research Network, a group of research centers that collaborates frequently, but each center has its own independent research enterprise--and its own IRB. The challenge was galvanizing the IRBs at all of our sites to embrace an alternative to the traditional IRB review process in which each site in a multi-center project reviews the project independently, often resulting in iterative and lengthy review timelines, and potentially conflicting modifications to the study protocol.

Two of our three deliverables pertained to "streamlining research review," wherein we had ambitiously proposed the creation of common IRB application forms and a network-wide centralized IRB platform as part of our original proposal. This scope was quickly determined to be infeasible in the project timeline. We stayed the course on our first deliverable, creation of a repository of site-specific IRB requirements, processes, forms, and related information. To gather this information, we interviewed each of the IRBs and formulated a web-based, searchable databank for each of the IRBs. This enables collaborators to anticipate review deadlines, application materials, and local stipulations or state laws that may affect the research. By reviewing these materials prior to IRB submissions, researchers can coordinate IRB submissions, avoid pitfalls, and ultimately speed the IRB approval process.

As part of the interview process, we gauged receptivity among all of the local IRB administrators to a centralized IRB, or a common form for HMO Research Network projects. IRBs varied widely in their endorsement of consortium-wide approaches, yet this still opened a channel for continued communication, and pursuit of alternative streamlining strategies to help both IRBs and researchers alike.

Coincidentally, national discussions about alternative models to the current IRB review system were taking place with broad participation by OHRP and other federal agencies, and representatives from across the research community. These contextual events, combined with the initial interviews undertaken by CCSN, help set the stage for an in-person meeting of all of the IRB administrators, which proved to be a watershed moment for the HMO Research Network. At this meeting, the sites agreed to pilot a facilitated IRB review process for minimal risk data-only studies. The approach entails having the project PI complete his/her local IRB's application form, which is prepared in consultation with the collaborating investigators at the sites. The lead IRB (i.e., where the project PI resides) reviews the project, and participating sites have an opportunity to either accept that IRB's review, or conduct an expedited (or full) review of their own. We have successfully piloted this process for three studies and have used the accumulated experiences to develop a draft standard operating procedure. This draft procedural document will be reviewed during the annual IRB workshop that is held in conjunction with the HMO Research Network's annual conference.

Getting to this juncture required careful attention to both overall (HMORN-wide) and individual sites' needs, and was predicated on the ability to openly discuss sociocultural and operational concerns, develop trust and a shared sense of purpose among groups who had very little interaction previously, and collectively reaffirm the overarching goals of this effort. Our experience has reinforced our optimism that both IRBs and researchers are committed to finding strategies to reduce barriers and create efficiencies in the research process.

Case Study #3 – Clinical Research in Critical Care
Principal Investigator: Alan Morris

"Reengineering Clinical Research in Critical Care" Scenario

We used an adequately explicit computer protocol to achieve a replicable method for blood glucose control with intravenous insulin in multiple intensive care units in hospitals in different cultures. The computer protocol (eProtocol-insulin) enabled different intensive care units to deliver clinical care and conduct intensive care unit research in a replicable manner. This directly addresses a major barrier to holistic clinical research – the low number of subjects in clinical studies. A computer protocol, located on a website accessible worldwide could enable a large multicenter laboratory using in all of its enrollment sites a replicable method. Such a laboratory might contain 5000 sites on several continents. It might enroll 200,000 patients within months. This would change the character of clinical research. One could imagine such a laboratory generating dose-response curves in humans and avoiding the pernicious secular changes in the clinical environment that plague current clinical trials. We propose tools such as our eProtocol-insulin could overcome these and other current barriers to holistic clinical research. In addition, eProtocol-insulin has joined adult and pediatric intensive care units in common research with a common and replicable method. It has overcome, in part, the barrier between adult and pediatric medicine.

Case Study #3 – ePCRN
Reducing Barriers to Community Participation in Clinical Research
Submitted by the ePCRN team - Principal Investigator: Kevin Peterson

Recruiting for clinical trials has become increasingly difficult in traditional research centers. Although potentially eligible patients who are willing to join a study may exist in the community, identifying a specific medically defined population in the community can pose particular challenges. Access to medical records for research purposes is prohibited by HIPPA and privacy concerns. Recruitment of subjects for research is therefore often limited to appeals to the general public through newspaper, television, and radio advertisements. These advertisements may miss appropriate participants, appeal to the wrong populations, or be limited in describing eligibility requirements in terms that are understandable to the lay public. This results in patients being unaware of potential high quality research opportunities, and in researchers struggling to find potential subjects. The ePCRN addresses these issues, and enhances opportunities for patients to participate in high quality research that has been screened and found appropriate for the patient by their primary care physician.

Case study

In the past recruiting for research has often included appeals to local medical providers. However in many community-based medical practices research pamphlets and posters sent by researchers are discarded or ignored. Even informational visits by researchers to local clinicians are quickly forgotten in the midst of the competing demands of a busy community practice. With the ePCRN architecture, researchers can describe eligibility criteria for a given study in detailed and standard medical terms. These descriptions are passed electronically to primary care practices, where they query a standardized multiple-disease registry based upon the Continuity of Care Record/Document (CCR/CCD) supported by a wide variety of electronic health records. With permission of the local research director, providers are electronically notified of all patients in the practice eligible for the study. A

provider can immediately determine who in the practice is eligible for a given study, or all the studies for which a patient is eligible. Any patient that the local physician identifies as appropriate is automatically contacted using email, text messaging, or a printed letter. Potentially eligible patients are provided with information about the study, can be referred to a website for more information, or be asked for permission to allow contact by the study investigator. Providers have the ability to identify and permanently remove any patient from participation or subsequent notification. The ePCRN provides opportunities for patients to know about relevant research, eliminates mass marketing, and ensures that the local clinician screens the potential research participation of every patient.

Case Study #3 – COG-PBMTC
Principal Investigator: Greg Reaman

Developing studies that compete for the same population has been a barrier to conducting research for the COG and PBMTC. The frontline COG and COG/PBMTC ALL and AML trials have transplantation as a component of the major study question. To account for potential negative effects on accrual, however, the trials have been designed to allow or encourage co-enrollment to transplant trials asking a hematopoietic source questions. The COG Stem Cell transplant member institutions, facilitated by the COG venue and infrastructure, are major participants and enrolling institutions in the BMT CTN pediatric trial (BMT CTN 0501: Multi-Center, Open Label, Randomized Trial Comparing Single Versus Double Umbilical Cord Blood (UCB) Transplantation In Pediatric Patients With High Risk Leukemia And Myelodysplasia) which is asking whether two cord blood units are superior to one cord blood unit for transplantation. Accrual to this trial is running ahead of projection.

Case Study #3– RIOS Net
Principal Investigator: Robert Williams

RIOS Net is a primary care, practice-based research network composed of clinicians practicing in medically underserved clinical and community settings, who voluntarily collaborate in studies aimed at improving the health and health care of their patients and communities. Most of the network clinicians practice in communities that are predominantly Hispanic or Native American. Four principal barriers to increasing research have been encountered:

Extensive IRB review processes – In addition to standard IRBs and IRB review processes, RIOS Net relates to two IRBs with jurisdiction over research conducted in Native American communities. These IRBs require an extensive set of community approval documentation prior to consideration of a research application (e.g., local health care providers and administrators, local community groups, tribal historical entities). These groups often meet infrequently, at considerable distance from the network central office, require presence at the meeting for discussion and approval, often require translation into a Native language, and may not achieve a necessary quorum for decision-making. In addition, these IRBs in their broader roles as tribal research review entities, impose a variety of conditions and restrictions on research conducted in their communities. While these processes are not inconsistent with the network's community-based participatory research philosophy, they do result in extended commitment of time and resources for research approval. The network addresses these requirements and expedites the processes through assuring research designs are culturally grounded, through early participation of key stakeholders in research selection and planning, through frequent communications with community groups, through

development of long-term partnerships with the community representatives, through staff with Native language fluency, and through experience with coordinating community reviews.

Infrastructure funding – In common with many other clinical research networks, the lack of stable infrastructure funding for network operations presents a barrier to efficient throughput of clinical research. Activities such as the community outreach described above or interproject network maintenance activities are not supported through current research funding mechanisms tied to specific, narrow research questions. Diversification of funding sources through addressing the interests of multiple stakeholders can provide a partial, but incomplete solution to this problem.

Varying community and clinical contexts – The wide variety of community and clinical contexts within which RIOS Net research is conducted, while strengthening the external validity of research findings, can present a barrier to research by increasing the difficulty in standardization of research protocols. The network has addressed this concern by incorporating flexibility in non-critical aspects of the research operation, while retaining standardization of key elements.

Insufficient numbers of content experts with experience/understanding of the primary care/underserved community environment – While the network functions as a large laboratory for translational research in primary care, its full utilization requires partnering with clinical topic-specific content experts who can work with network leadership and members to design appropriate studies for the network. Unfortunately, the number of such content experts who have experience and/or understanding of the primary care environment and who are able to refine important research questions to be testable in the network laboratory are relatively few. This mismatch between the relatively large network laboratory capacity and the number of researchers capable of utilizing the laboratory presents a barrier to research. While the network leadership works to recruit and "train" content experts for that role, the process requires a level of flexibility and time commitment from the content expert that may not be appealing to them.

CASE STUDY #4 – DISSEMINATION OF KNOWLEDGE INTO PRACTICE

Group Members: Eric Larson (CCSN)-Lead, Robert Harrington (CTN), Robert Williams (RIOS)

Group Topics:

- **Best Practices**
- **Partnering ouside the network**
- **Cross-fertilization**
- **Communication**

Case Study #4 – MCRC
Principal Investigator: Lee Green

The MCRC conducted a prospective cohort study of the incidence and prevalence of depression symptoms among patients with coronary heart disease (CHD) in primary care practices, as a demonstration of the effectiveness of the Collaboratory infrastructure. The project included administering the PHQ-9 depression symptom questionnaire to all enrolled CHD patients at study entry and at least quarterly thereafter. Practices could also request

that the system print out a PHQ-9 at time of visit for all CHD patients, even if they were not enrolled in the study, with the data simply not forwarded to the research database. Use of the PHQ-9 in the course of the study increased the practices' attention to and awareness of the risk of depression among CHD patients, and led to the diagnosis of several new cases of significant depression. It resulted in the detection of one suicide risk that would have otherwise gone unnoticed, with appropriate urgent intervention provided. Some of the practices are continuing to screen for depression after the study.

The literature going back to the original diffusion-of-innovation studies of Rogers et al. has shown that trialability, the ability to try out an innovation with successful results and no difficulties or disruptions, is an effective aid to dissemination into practice. Our experience with depression screening, while not intended as a demonstration of this effect, is consistent with the diffusion and dissemination literature. It suggests a substantial direct benefit may accrue to patients in Type II translation research.

Case Study #4 – AGNIS
Principal Investigator: Dennis Confer

AGNIS leadership team: Dennis Confer, Mary Horowitz, Doug Rizzo, Martin Maiers, Ken Bengtsson and Paul Zyla.

AGNIS (A Growable Network Information System) is an open-source project of the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR). NMDP and CIBMTR touch a large network of more than 400 hematopoietic cell transplant (HCT) programs spread through more than 60 countries. About half of these HCT programs are in the U.S. and were dramatically impacted by passage of the Stem Cell Therapeutic and Research Act of 2005. Among other things, the Act established a national database, the Stem Cell Therapeutic Outcomes Database (SCTOD), to collect outcomes data from every allogeneic HCT with a recipient or donor in the U.S. A contract to establish and manage the SCTOD was awarded by the Health Resources and Services Administration to CIBMTR in September of 2006. Among many tasks, the contract required CIBMTR to reduce the data submission burden for transplant teams and to offer an electronic data capture (EDC) system. CIBMTR chose to implement an EDC solution using a proprietary web-based data management system (FormsNet™) and AGNIS. The goal is to allow flexibility, but reduce redundant data entry. Many transplant teams will choose to enter data using FormsNet and use AGNIS to back-populate a local database. Others, particularly large programs, will enter data into a local database and use AGNIS to forward populate FormsNet.

Faced with the rapidly changing environment of HCT data management, the American Society for Blood and Marrow Transplant (ASBMT) together with CIBMTR and NMDP sponsored an IT Summit for transplant teams in January of this year. The Summit featured presentations on FormsNet, AGNIS, caBIG, caDSR and a variety of approaches for addressing HCT data management. Breakout sessions addressed data standards, data collection, data sharing and security/confidentiality. One-hundred-forty IT and data management personnel from U.S. and international transplant centers attended the one and one-half day Summit. In post-meeting surveys, overall content of the Summit was rated 4.4 on a five-point scale (with 5 as the highest rating). Ninety-five percent of respondents indicated that they would suggest IT program enhancements at their facilities. Asked if the meeting should be repeated, 99% said “Yes”. Although we have distributed information

through many avenues, the focused IT Summit proved to be a highly effective mechanism for disseminating knowledge into the hands of users. We anticipate the Summit will propel many HCT centers to adopt improved practices for efficient, comprehensive data management.

Case Study #4 – CTNBP
Principal Investigator: Robert Harrington

The Clinical Trials Networks Best Practices (CTNBP) team, including its Study Coordinator Advisory Committee (SCAC), spent a good portion of the first year of the Roadmap contract (2004-05) collecting information, tools, and templates the team felt would assist research sites with implementing clinical trials. The team organized information into an easy-to-navigate Web site (www.ctnbestpractices.org) has proven to be valuable to the industry and gives much-needed support to some of the smaller research shops new to conducting clinical research. In January 2006, most of the Web site was opened to the public.

The specific example we are going to use for this case study is a Clinical Research Coordinator (CRC) training program put into place about two years ago by a member of the CTNBP SCAC, Kimberly Broadway, RN, BSN, who works at The Heart Center in Huntsville Alabama. When she started in her department, Ms. Broadway interpreted its training philosophy as, “Here you go. Here are your studies. Sink or swim.” Since then, Ms. Broadway has implemented a solid, sustainable training program at The Heart Center using the online training modules, tools, and templates housed on the CTNBP Web site.

As part of the new training program, each employee-trainee is given a copy of the book Lessons from a Horse Named Jim, published by the Duke Clinical Research Institute. After reading the book, trainees complete several training modules available on the CTNBP Web site: Clinical Research Introduction (based on Lessons from a Horse Named Him), Human Research Subject Protection, Good Clinical Practice, Keys to Building a Successful Research Site, Essential Regulatory Documents, and What Is a Clinical Research Study? Some trainees complete therapeutic-area training on the cardiovascular system, acute coronary syndrome, and congestive heart failure.

According to trainees, the most useful tool on the Web site is the Coordinator Training Checklist, which outlines each task a study coordinator should understand for each specific study. Ms. Broadway has expanded the checklist to include site-specific SOPs.

The training program has yielded competent employees who possess the skills necessary to conduct well-organized clinical-research studies. Having a solid training program in place, a departure from the old “sink-or-swim” method, has fostered a team environment with clear expectations regarding job responsibilities and expectations. This, in turn, has gone a long way to ensure The Heart Center can carry out its mission to promote excellence in clinical research.

Case Study #4 – InterTrial Project in the Clinical Trials Network at Columbia Univ
Principal Investigator: Stephen Johnson

Collaboration to Disseminate Knowledge Needed to Conduct Research Protocols

The concept of dissemination of knowledge into practice can be expanded to include dissemination of knowledge about clinical research. A crucial issue in community-based research is dissemination of knowledge about how to conduct research in accordance with

the protocol. Our group experimented with a variety of technologies to facilitate this process. We used a web-based collaborative work system (WebEx) to hold web conferences (synchronous) to train investigators and coordinators in our Clinical Trials Network about the details of protocols being deployed. We also experimented with wikis, using this tool as a forum for coordinators to post questions about protocol issues or study procedures and to support communication (asynchronous) between clinical sites and the Research Support Hub of the network. This tool also fulfilled a need voiced by many coordinators who wanted to communicate with other coordinators conducting the same protocol(s) or to discuss study problems and jointly seek the best solutions. The platform was effective for disseminating training in good clinical practice (GCP), standard operating procedures, announcements about the network and related news. Web 2.0 technologies such as wikis, blogs, podcasts, and online video streaming have the potential to allow coordinators, investigators, and other stakeholders to collaborate, create content, share knowledge, and subscribe to updates of interest. While these possibilities are exciting, considerable effort is needed to provide appropriate levels of training and support to realize technology's potential.

Case Study #4 –CNICS
Principal Investigator: Jim Kahn

The Dissemination of the accumulated knowledge is based on the ongoing manuscripts that we are working on from this project. That dissemination of knowledge also led us to develop a web site for a clinician to enter data from the field and see how the viral isolate is different or the same compared with other viral isolates in our database. This has not gone well since clinicians are unlikely to take the time to enter data. A better approach would be to allow clinicians to populate our public database electronically with the genotypic or phenotypic data from their patients. We are working on this solution too.

Case Study #4 – CRN Harmony
Principal Investigator: J.Richard Landis

The deployment of information technologies in support of clinical trial research is essential to facilitating the process of moving research findings into meaningful clinical outcomes. Dissemination of knowledge across research teams in the use of research technology is an important element in this process.

Oracle applications provide an integrated suite of informatics tools and architecture needed in the development of clinical study data management systems for national multi-center studies and single center clinical studies. The knowledge and experience gained by the Penn Roadmap technical team in the use of Oracle Clinical applications was shared with the information systems staff of the University of Pennsylvania Abramson Cancer Center to assist in the development of a data management system for a new cancer clinical trial. This knowledge transfer and exchange of research information technology contributed to a more efficient and timely development of a novel phase II cancer study.

In addition to the development of clinical trials, Oracle applications have been utilized to enable research oversight activities and investigator information access and exchange. Integration and access to blinded clinical trials information was made possible through the use of portals for study Data Safety Monitoring Boards. Oracle supported study specific web sites were developed to provide investigator access to study protocols, forms, publications, meetings and planning information.

Knowledge dissemination in the use of research tools, methods, and techniques helps to promote and strengthen research quality and outcomes.

Case Study #4 – The Coordinated Clinical Studies Network (CCSN)
Principal Investigator: Eric Larson

Assessing Barriers and Facilitators to the Effective Translation of Research into Clinical Delivery Systems

The CCSN is comprised of sites in the HMO Research Network, a group of research centers that frequently collaborate. Each member of the HMO Research Network is an independent research enterprise linked to a 'parent' integrated health care delivery system. While dissemination of local research results into practice at the parent health plans is assumed to occur in every location, a Network-wide examination of translation practices to identify opportunities and best practices had never been carried out.

To obtain a more complete understanding of research translation at each site, phone interviews with senior researchers and health plan leaders at 13 of the 15 members of the HMORN were conducted. Organizational characteristics and factors related to relative success of translating research into practice (TRIP) were identified. A scoring system was created to identify the extent to which successful translation of local research findings into practice occurred in the parent health plan.

We identified 5 facilitators for successfully translating of local research results into practice at the health plans:

1. **Quality and types of communication between the research center and delivery system**. Communication was enhanced when the health plan had a "champion" promoting specific research. It was found that personal relationships between researchers and delivery system leaders cultivated the best lines of communication.
2. **Level of delivery system involvement in interventional research**. Delivery system leaders perceived a higher degree of "value" when intervention studies were directly linked to quality initiatives.
3. **Degree of delivery system consultation offered by research centers**. The health plans highly valued those research centers providing consultative services (e.g., clinical trials, quality initiatives, experimental design and analysis, evaluation of programs, database design and maintenance, and medical informatics).
4. **Publication of research results and study outcomes**. Such dissemination was especially valued among health plans linked to academic associations.
5. **Presence and significance of motivating factors**. For delivery systems, impact on quality initiatives was most significant incentive to translate results into practice. Researchers were primarily motivated by intellectual and professional growth.

The primary barriers to translation were (1) time demands on both parties, and differing research and business timelines for access to results; (2) communication issues related to time constraints, lack of awareness, and business-culture variation; (3) change management; and (4) differing priorities.

The HMO Research Network (HMORN) is an excellent laboratory for translating research into practice. It comprises a diverse group of health care delivery systems typical of the US.

Although significant limitations exist, this assessment suggests several mediators, facilitators and barriers that may be important in scaling-up research translation efforts on a broader level in US delivery systems.

Case Study #4 – Clinical Research in Critical Care
Principal Investigator: Alan Morris

"Reengineering Clinical Research in Critical Care" Scenario

We used an adequately explicit computer protocol (eProtocol-insulin) to translate research results to clinical practice. The computer protocol (eProtocol-insulin) enabled different intensive care units to deliver usual clinical care in a replicable manner close to that achieved in the developmental research unit (LDSH eProtocol). eProtocol-insulin is driven by patient-specific input data and displays treatment recommendations intended to bring the patient's blood glucose within the 80-110 mg/dl target range.. This computer protocol enabled 7 usual care hospitals to replicate the behavior of the research site (LDS eProtocol). eProtocol-insulin enabled translation of research results to usual clinical practice by exporting the computer protocol method to clinical practice sites. Modification of eProtocol-insulin to incorporate educational material that might satisfy continuing medical education requirements could make it or similar compouter tools a point-of-care education method.

Case Study #4: Communication – ePCRN
Submitted by the ePCRN team - Principal Investigator: Kevin Peterson

Introduction

Close communication is necessary for close cooperation. Access Grid (AG) is an Internet2-driven, high performance audio-visual conferencing technology used worldwide by academic and government organizations to enhance communication, human interaction, and group collaboration. Most commonly used interactive video and audio systems operate at less than 384Kbps and do not have the capacity for real time audio and visual communication. AGN technology provides missing elements of whiteboards, application sharing, and multi-site conferencing that promote more efficient group-to-group communications between the study investigators. Monthly videoconference meetings between the University of Minnesota, UCSF, and Birmingham, England and ten US academic centers have allow closer communication at reduced cost, promoting complimentary and cooperative roles among the investigators.

Case study

Previous communication technology has been limited to telephone conversations, or face to face meetings, increasing cost and limiting international cooperation. The ePCRN has installed tailored installations of AGN technology in ten participating Practice-Based Research Networks (PBRNs) located in US academic centers and in three sites in the United Kingdom. This has allowed one to two conferences per week between the US and the UK, enabling a previously unattainable level of international cooperation in the development of computer models and software. Additional conferences between participating regional PBRN research directors within the US has promoted the development of a single national perspective on the development of a model for the performance of clinical research in Practice-Based Research Networks (PBRNs). The

principle problems identified in the implementation in medical environments of this valuable communication technology have been identified and initial solutions identified. Although additional work is needed in simplifying the use of this technology to make it more easily accessible to unfamiliar users, the ability to communicate both audio and visually in real time provides a valuable step forward in the development of both national and international collaborations.

Case Study #4 – COG-PBMTC
Principal Investigator: Greg Reaman

There are several best practices and achievements that highlight the collaboration between the COG and PBMTC. The ones noted for dissemination of knowledge into practice include building websites for the BMT clinical trials developed and supported through the COG infrastructure, joint publications, and employment of the same non-profit fiscal agent to manage funds for both the COG and PBMTC. As for all COG studies, websites are developed to give members access to each COG study. The most current version of the approved protocol, case report forms and relevant communication are posted, and updates are provided weekly, if needed. For the three clinical trials that were developed as a result of the COG-PBMTC collaboration (ASCT0521/SUP051, ASCT0431/ONC051, and ASCT0631/SCT051), a website was also developed for each study, and access is granted to the 6,000+ members of the COG. Joint publications are also in development, highlighting the success of the COG-PBMTC collaboration, which may provide useful information for other organizations wanting to expand their networks. Currently, the National Childhood Cancer Foundation (NCCF) serves as the agent that manages funds for both the COG and PBMTC. It is advantageous to manage the research funds with only one organization to optimize efficiency in contract and finance management.

Case Study #4 – RIOS Net
Principal Investigator: Robert Williams

RIOS Net is a primary care, practice-based research network composed of clinicians practicing in medically underserved clinical and community settings, who voluntarily collaborate in studies aimed at improving the health and health care of their patients and communities. The nature of these clinicians, their practices, and their communities creates an environment in which the dissemination of knowledge into practice is integral to the network's philosophy of focusing on translational research and on community-based participatory research. The network is directed by its members and community representatives and focuses its research on clinical topics that the membership and community representatives have determined to be priorities. This focus on research that the clinicians and communities have prioritized and a related focus on feasibility of innovation sets a context of receptivity to incorporating findings into practice, perhaps the most important aspect of the network's approach to dissemination of knowledge into practice. In addition, the focus on research that is relevant to clinicians is particularly important given the under resourced nature of many of the practices and communities, and the voluntary aspect of clinician participation in the research (i.e., network participation is not driven by central delivery systems).

RIOS Net conducts educational activities for both clinicians and community members aimed at incorporating research findings into practice and into broader community health improvement. On the professional side, we interweave education into each aspect of the

research process and network activities. The overall approach is to provide targeted, relevant clinical knowledge and guidance, together with local and overall research data findings, and feasible strategies for incorporating new information into practice. Examples of some of the clinician educational strategies used include:

- One-on-one, in-practice meetings with network outreach specialists
- Training for participation in specific research projects that includes presentation of project/topic-related content information and, in some cases, assessment of knowledge acquisition
- Web-based modules presenting brief content information on the specific and broad topic of research projects
- Summary reports of practice, local, and overall network research results provided both in-person and via a secure web-page
- Brief printed summaries of research findings with advice regarding practical application of study results
- Didactic and interactive presentations at member meetings
- Training in clinical skills and providing information on resources to support screening and intervention activities related to priority topics
- Provision of CME credit for multiple elements of network activities, consistent with new CME guidelines

While not directly related to dissemination of knowledge into practice, on the community side, the network conducts educational activities with groups in communities throughout New Mexico aimed at providing background information on priority topics and research results. These presentations are integrated with the network's partnership with the communities in research development and conduct. Their purpose is to disseminate information for communities to use in addressing health problems on a broader scale. In a related development, we have recently obtained funding to develop feasible models for clinicians to be able to use research results to inform development of local and state health policies.

While assessment of the effectiveness of these strategies for disseminating knowledge into practice has not been a focus of RIOS Net's work to date, limited data are available. Following research projects examining risk of development of diabetes in patients seen in network practices, short and long term followup clinician surveys coupled with qualitative interviews of clinicians reveal that as a result of participation in these network studies, clinicians were substantially more likely to subsequently engage in diabetes prevention activities with their patients at risk for diabetes.

The principal challenge to these approaches to knowledge dissemination is maintenance of infrastructure funding. However, we have found increasing understanding of the importance of "the feedback loop" among various stakeholders, with associated interest in funding.

Case Study #4 – IECRN
Principal Investigator: Steve Durako

The Development of the Clinical Research Network Inventory (IECRN project)

The Inventory and Evaluation of Clinical Research Networks (IECRN) is part of the Reengineering the Clinical Research Enterprise component of the Roadmap, which seeks to enhance the efficiency and productivity of clinical research by promoting clinical research networks. The IECRN was charged with identifying all clinical research networks (CRNs) worldwide and collecting information about their nature and scope. These data are available as "network profiles" on a public website at https://www.clinicalresearchnetworks.org. The purpose of the web-accessible Inventory is to promote the existence of these networks, to facilitate interactivity among the networks, and to increase accessibility to the clinical research community. One of the first project challenges was to clearly define the characteristics of clinical research networks (CRNs) so that eligibility criteria could be established. A general definition provided by NIH was refined as follows: (1) "clinical" was interpreted to mean "health-related in humans," including epidemiology, behavior modification, health communication, patient care, medical practice, clinical quality improvement, and clinical process improvement research; (2) only existing networks were included; (3) a network had to have scientific leadership; (4) an association of entities formed with the explicit intent of being a continuing network to conduct multiple research studies was eligible regardless of how many studies it had conducted; (5) a network must include at least 3 participating entities, and at least 3 of the entities had to be independent or semi-independent from each other. The data from the instrument known as the Core Survey were used to populate the Inventory. Data collection began in August 2005 and is ongoing, though the majority of networks were found and included by the end of March 2006. As of March 2008 there are 274 network profiles in the Inventory. Each network profile includes the following information (by permission of the network): year network established, funding sources, geographic coverage, participating entities, types of studies conducted, diseases and conditions studied, and special population focus. The Inventory has been available on the website for approximately 2 ½ years (since October 2005). Westat is currently working with NCRR on dissemination activities to more effectively position the website (particularly the Inventory) as a resource for the CRN community. These activities include enhancements to make the website more user-friendly and more appealing (underway), posting an on-line website user satisfaction survey (recently submitted to OMB), and developing a paper to describe the accomplishments and findings of the IECRN (in development). Currently the focus is on the usefulness of the Inventory data rather than on the IECRN project. The challenge is to learn more about the information needs of the clinical research community, as well as whether they are aware of the existence of the Inventory and, if so, whether it is useful to them. The survey data will provide information on what users are looking for on the website, how they intend to use the information they find, and how satisfied they are overall with the Inventory. The plan is to promote the Inventory by contacting CRNs with active websites to request posting of the website link on their network webpage, and by broadcasting new Inventory website information (updated profiles, new networks, enhanced website capabilities, etc.) to those who have signed up to receive this information. Our goal for these dissemination efforts is to expand the website Inventory and, by facilitating relationships and partnership-building, indirectly accelerate medical discovery to improve health and speed translation of scientific discoveries into practice.

Michigan Clinical Research Collaboratory
MCRC

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Lee Green MD, MPH

Clinical Research Information Fabric:

Honest Broker Demonstration Script
Center for the Advancement of Clinical Research

University of Michigan Medical School
Ann Arbor, Michigan

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATORS

Lee Green, MD, MPH
Professor and Associate Chair for Information Management
University of Michigan Department of Family Medicine
University of Michigan Center for the Advancement of Clinical Research

Dr. Green is Professor and Associate Chair for Information Management in the Department of Family Medicine at the University of Michigan. He is Director of the Great Lakes Research Into Practice Network (**GRIN**), a statewide practice-based research network of over 140 primary care practices focusing on clinical (phase II) translational research. He is also Associate Coordinator of the Decision Consortium, an interdisciplinary seminar on decision making issues at the University of Michigan, involving faculty and graduate students from psychology, business, medicine, nursing, engineering, law, philosophy, public health, and others.

Dr. Green's primary interest is in the cognitive aspects of physician practice change, and their implications for improving the quality of routine primary care practice. He has a long record of involvement in and leadership of clinical practice guidelines development and implementation, nationally and locally. His other interests include use of information support to improve quality of primary care, maintenance of practice based research networks, office treatment of hypertension, and outcomes of asthma management.

CO-INVESTIGATORS

Daniel Clauw, MD
Assistant Dean for Clinical and Translational Research

Dr. Clauw oversees a multidisciplinary group that performs both mechanistic studies and clinical trials in overlapping conditions characterized by chronic pain and fatigue, including fibromyalgia, chronic fatigue syndrome, and Gulf War Illnesses. Dr. Clauw has been the P.I. of NIH and Department of Defense grants studying this spectrum of illness continuously since 1994. The Center currently has several million dollars per year in federal funding to study these disorders. Dr. Clauw and his group have been instrumental in establishing that the systemic conditions noted above, and regional pain syndromes such as interstitial cystitis, low back pain, and irritable bowel syndrome all have common pathogenic and clinical features. One of the primary areas of interest of his group has been in studying sensory processing in these conditions, and in demonstrating that many patients with these conditions have a widespread disturbance in pain processing. Current work is establishing the nature of the central pain processing abnormality in these conditions, using a variety of approaches, including functional MRI. Dr. Clauw also directs the Center for the Advancement of Clinical Research (CACR) at the University of Michigan. The CACR provides infrastructure and support for clinical and translational research for the Medical School from protocol development through subject recruitment, performance, and monitoring of study conduct, to data management and analysis.

John F. Greden, MD
Executive Director, University of Michigan Comprehensive Depression Center

Dr. John Greden is Executive Director of the University of Michigan Comprehensive Depression Center, the Rachel Upjohn Professor of Psychiatry and Clinical Neurosciences in the Department of Psychiatry, and Research Professor in the Molecular and Behavioral Neuroscience Institute. He joined the faculty at the University of Michigan Medical School in 1974 and served as Chair of Michigan's Department of Psychiatry from 1985 to 2007 when he stepped down to focus on directing the Depression Center. He has more than 27 years of NIH funding as investigator, co-investigator or consultant. His research has focused on the lifetime course of depression and bipolar disorders with an emphasis upon brain mechanisms and clinical comprehensive interventions to prevent recurrences. In 2001, Dr. Greden established the University of Michigan Comprehensive Depression Center, the first of its kind in the nation and a multidisciplinary prototype for integrating research, clinical care, education and public policy. He has emphasized the importance of working collaboratively among medical centers of excellence, such as in the Michigan Clinical Research Collaboratory (MCRC). Dr. Greden is leading efforts to catalyze depression centers throughout the country and integrate them into a National Network of Depression Centers (www.NNDC.org) comparable to the National Network of Cancer Centers, thus enabling large-sample studies, stronger voices in overcoming stigma, and national education efforts.

PROGRAM DESCRIPTION

This project will construct, test, refine, and progressively extend a common infrastructure linking three existing practice-based networks with two University of Michigan research centers. The five components include: 1) GRIN, a statewide network of community primary care physicians; 2) MCORPP, a community hospital-based Cardiovascular Network; 3) Depression Primary Care Network; 4) Cardiovascular Center, and 5) Depression Center. These networks and clinical research centers currently use dramatically different human and IT systems to perform research. The infrastructure that each utilizes will be re-engineered emphasizing both "human" procedures -- those necessary to perform high-quality and compliant clinical research in multiple community-based practices -- and information technology (IT) systems.

A Feasibility Project will assess treatment responses, recurrences, rehospitalizations, mortality and costs for those with co-occurring cardiovascular and depressive disorders when compared with those having only cardiovascular problems. This project will be rolled out in a staged fashion and new research centers and primary care networks will be progressively added in future years, starting with the Women's Health Center and Cancer Center. The result will be a new integrated enterprise --- the Michigan Clinical Research Collaboratory (MCRC).

PROGRAM ACCOMPLISHMENTS

The MCRC project's accomplishments were achieved in four areas: 1) Secure interconnection of clinical and research information systems within and across institutional boundaries. 2) HIPAA- and IRB-compliant data exchange with clinical data and research

data appropriately segregated and routed. 3) Open-standards-based lexical mapping of data between systems created for different purposes. 4) Use of the infrastructure for a clinical study in community practices, integrating research into routine workflow.

1) A combination of open-source tools for SOAP messaging and dual-certificate-authenticated ssl connections were used to build a transport- and session-layer infrastructure for highly secure communication and interaction between a clinical care support system at the UM Depression Center (MDOCC), a clinical reminder system in community practices (ClinfoTracker/Cielo Clinic), a research registry system in the Cardiology division (BMC2), a clinical trials management support system (Velos eResearch), and the Honest Broker that tied them all together.

2) The Honest Broker received information on acute coronary interventions from BMC2 and passed it to primary care physicians via ClinfoTracker, and exchanged information in both directions on depression management between MDOCC and ClinfoTracker. It passed only the subset of data used for the research study, and only for those patients who consented, to Velos, and received and acted on data requests from Velos to manage study patients per protocol. The research protocol was conducted with no one outside the primary care practices actually knowing the identities of the patients. It mapped patient identities between the systems, which used different identifiers, with high probability and had the primary care practices confirm the matches.

3) The Honest Broker used SNOMED-CT and LOINC in conjunction with the semantic expressiveness of HL7 Clinical Document Architecture (CDA) to map concepts in over 100 demographic and clinical data points, between the systems involved, producing meaningful data to transfer for clinical care and for research. The project worked with Regenstrief Institute staff to extend LOINC to include the Pfizer PHQ-9 depression screening instrument,

4) The Honest Broker passed data to and from ClinfoTracker clinical reminder systems in four non-academic community practices in a practice-based research network (PBRN) that participated in the prospective cohort study of incidence and prevalence of depression symptoms in patients with coronary heart disease. The sites differed widely: one urban and one rural clinic for the underserved, one large urban family practice with a wide range of patients, and one very busy medium-sized suburban family practice. The study was conducted with the entire support infrastructure invisible to the sites; the study recruitment materials, forms, and data collection instruments appeared as specified by the research protocol just as though they were clinical reminders for routine services (e.g., diabetic eye exam referrals). Patients were offered enrollment automatically, once only, if eligible. This approach achieved a study enrollment rate of over 70% of all potentially eligible patients.

A Project of the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR)

AGNIS

HHSN268200425215C

Dennis Confer, MD

A Public System for Electronic Exchange of Clinical Network Data:

A Collaborative Effort of the
Center for International Blood and Marrow Transplant Research (CIBMTR)
and the National Marrow Donor Program (NMDP)

Minneapolis, MN

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Dennis L. Confer, MD
Chief Medical Officer
National Marrow Donor Program (NMDP)

Dennis L. Confer, MD began a consulting role with the National Marrow Donor Program (NMDP) as interim Medical Director in 1991. He became Medical Director in 1993, and in 1996, began a full-time appointment with the NMDP. He was named Chief Medical Officer of the NMDP in 1999.

Dr. Confer was the Director of Marrow Transplantation at the University of Oklahoma from 1991 to 1996. He attended medical school and completed his internal medicine residency at the University of Nebraska Medical Center and performed his fellowship training in hematology and oncology at the University of Minnesota.

PROGRAM DESCRIPTION

AGNIS: A project of the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR).

Dennis L. Confer (PI)[1], Mary M. Horowitz[2], Douglas Rizzo[2], Ken Bengtsson[1] and Martin Maiers[1]. [1]NMDP, Minneapolis, MN. [2]CIBMTR, Milwaukee, WI.

AGNIS is a public system that facilitates controlled, automatic and secure sharing of authorized data between multiple, dissimilar database systems. AGNIS eliminates multiplicative data entry activities because data will enter the electronic network once with AGNIS facilitating subsequent distribution and synchronization between databases. AGNIS software, distributed under a public license at www.agnis.net, must be installed at each participating node in an AGNIS network.

AGNIS has been developed using and building upon open source tools available from the National Cancer Institute's (NCI) caBIG effort and other well supported projects. caBIG provides core functionality for what is called "grid computing", meaning that organizations connected together on a grid or network can search and access other data on the same grid. Related projects provide security, encryption, data storage and code building toolsets that have been incorporated into AGNIS. The data communicated by AGNIS are specified by collections of data elements, defined and managed in the NCI cancer Data Standards Repository (caDSR).

The sponsors of AGNIS are the NMDP and CIBMTR. The sponsors collaboratively facilitate multi-center research in hematopoietic stem cell (HSC) transplantation through systematic prospective data collection and through sponsorship/management of multi-center clinical trials. More than 450 HSC transplant programs, many with their own electronic databases, submit data to the databases of NMDP or CIBMTR and these programs comprise the user base of AGNIS.

PROGRAM ACCOMPLISHMENTS

Aims of the Contract:

Aim #1: Establish a model for clinical data exchange within and between networks

The first aim of this study was to establish a model for exchange of clinical data within and between clinical research networks involved in HSCT. This model includes:

- Creation of a governance structure;
- Establishment of business rules;
- Development of a data dictionary; and
- Definition of a robust, platform-independent messaging system.

Aim #2: Implementation of clinical data exchange

Implementation includes:

- A messaging exchange between the CIBMTR (formerly known as the IBMTR) and the NMDP;
- A messaging link extension of the above to a major U.S. transplant center, the University of Minnesota; and
- A messaging link extension to at least one international clinical data registry.

Aims Completed:

Creation of a governance structure.

A governance structure was created to oversee, advise and aid in the evolution of the project. This structure consists of an Executive Committee, comprised of the investigators; an international Advisory Committee of clinical experts and a Technical Committee of information technology experts. A Data Safety Monitoring Board (DSMB) was also created to advise on the issues of patient data confidentiality and consent.

Establishment of business rules.

Business rules were developed to determine the level of application security necessary, access to data, required message header data and the requirements of return messaging. These rules guided the development process and determined which open source security tools were used, such as open SSL and site certificates for security and XML for message structure.

Development of a data dictionary.

Prior to funding, the project leaders, NMDP and CIBMTR, had initiated an effort to harmonize their similar, but distinct data collection forms. The AGNIS project and a subsequent contract from the Health Resources and Services Administration to develop the Congressionally mandated Stem Cell Therapeutics Outcome Database (SCTOD) galvanized the harmonization effort. Using the newly developed harmonized and Transplant Essential Data (TED) forms as a base, approximately 11,000 common data elements (CDEs) for HSCT transplant are in the process of being curated on the publically available cancer Data Standards Repository (caDSR). The caDSR is a part of

the NIH cancer Bioinformatics Grid (caBIG™) project. These CDEs are the building blocks of the messages used by AGNIS to communicate between institutions and are expected to be the basis of HSCT collected data for the future.

Definition of a robust, platform-independent messaging system.

AGNIS is an open source application which makes use of other open source technology developed for and by the caBIG project. Written in Java, AGNIS uses the security model of Globus®, the group management properties of Grouper™, messaging aspects of the caBIG project and takes advantage of other well known and active open source applications. This model of development allows for high quality code that is current with today's standards.

A messaging exchange between the CIBMTR and the NMDP.

The AGNIS system has been implemented at the CIBMTR Milwaukee and NMDP Minneapolis sites. This system allows the CIBMTR to query for completed forms data which is then loaded into the research and SCTOD databases. All data collected by the NMDP from AGNIS is sent to the FormsNet™ 2.0 application for data validation. Although FormsNet 2.0 is not covered under this contract, it is an integral part of the form submission and validation process.

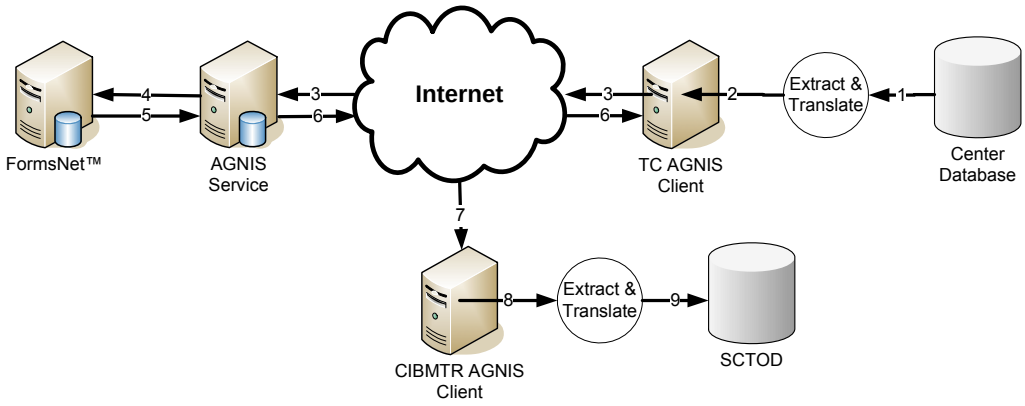

Figure 1

A messaging link extension to a major U.S. transplant center.

CIBMTR and NMDP approached the University of Minnesota, MD Anderson Cancer Center and StemSoft Software, Inc. about becoming involved with the AGNIS project as early adopters. Through regular weekly technical meetings, these early adopters provided valuable insight on every aspect of the project. MD Anderson was able to include AGNIS functionality into their in-house BMTweb software. StemSoft made the decision to use FormsNet 2.0 as their data entry system and have their BMTbase™ software use AGNIS to extract the data back into the site's StemSoft database.

A messaging link extension to at least one international clinical data registry.

It was expected that a connection with the EBMT's PROMIS system would be in place by the end of the contract. However, due to resource limitations at the EBMT site in England, this goal is not expected to be realized until 2008.

TB Trials Network

TBTN

Enhancing the U.S. Public Health System's Willingness
and Capacity to Engage in Clinical Research

Contract # HHSN 268200425214C
ADB Contract No. N01-HC-45214

Carol Dukes Hamilton, MD

Duke Clinical Research Institute
Duke University Medical Center
Durham, NC

BRIEFING BOOK SUMMARY

May 8, 2008

Link to web site of Program or Institution:
www.tbtrialsnetwork.org
http://www.dcri.duke.edu
https://www.tbtrialsnetwork.org/tbtc

PRINCIPAL INVESTIGATOR

Carol Dukes Hamilton, MD
Associate Professor of Medicine
TB Trials Network (TBTN), Duke University

Dr. Carol Dukes Hamilton is an Infectious Diseases-trained Associate Professor of Medicine at Duke University Medical Center, whose research program focus is to optimize strategies to diagnose, cure and prevent development of tuberculosis (TB). She has a special interest in TB in HIV-infected individuals and her clinical outpatient work is largely comprised of patients with HIV/AIDS. She is actively involved in both clinical trials and epidemiologic studies. She currently has independent research support and has a history of consistent research support over the years from the NHLBI, NIAID, NIEHS, the VA Career Development Program, and the U.S. Centers for Disease Control and Prevention (CDC). She is also a current recipient of NIH Roadmap funding to improve interoperability among clinical research networks. In this context, she is working on projects to improve data standardization in the therapeutic area of TB, focusing on TB research needs, as well as improved processes for human subject protection and consent. Dr. Hamilton has taken numerous opportunities to practice medicine and perform clinical research in resource-poor countries. She spent 8-16 week stints in rural Zimbabwe (1987), in urban Tanzania (1989), and as a visiting professor in urban Saudi Arabia (1995). In 1995, Dr. Hamilton and other CDC-funded investigators began a multi-center TB trial of a new drug, rifapentine. The investigator-driven consortium resulting from the rifapentine trial (Study 22) became known as the TB Trials Consortium. The Consortium provided a base from which Dr. Hamilton's other TB activities have grown. In 2001 Dr. Hamilton became the Medical Director of the North Carolina TB Control Program. Her role in the statewide public health management of TB activities enhances her work with other public health-oriented TB specialists in the U.S. and internationally. It also provides outstanding opportunities for epidemiologic and programmatic research for her and her trainees. More recently, Dr. Hamilton has used the State's TB Control program as the basis for a collaboration with colleagues at the Duke Center for Human Genetics. They successfully competed for an NHLBI R01 to support collection of DNA from proven pulmonary TB patients in North and South Carolina, as well as in Buenos Aires, Argentina. Dr. Hamilton and her genetic epidemiologist collaborator, Dr. William Scott, are investigating candidate genes that may contribute to human susceptibility to TB. Dr. Hamilton is currently leading a study of TB diagnostic strategies in Moshi, Tanzania, funded by the NIH ISAAC project.

PROGRAM DESCRIPTION

The TB Trials Network Roadmap Project operates under the direction of Carol Dukes Hamilton, MD, of Duke University Medical Center. The project involves the collaboration of multiple institutions and over 120 experts in the area of Tuberculosis (TB) and clinical trial networks.

Members of the Tuberculosis Trials Consortium (TBTC), the Centers for Disease Control and Prevention (CDC), and the Duke Clinical Research Institute (DCRI) are the underpinnings of the project. The TB Trials Consortium (TBTC) is a network of U.S.-based academic and federal investigators who have been engaged in TB-related clinical research since 1993. The TBTC is funded by the Centers for Disease Control and Prevention (CDC), and includes 21 U.S. sites, three Canadian sites and single sites in Brazil, Uganda, South Africa and Spain.

The major focus of the proposed projects will be to enhance the willingness and capacity for clinics within the U.S. public health system to engage in clinical research. Though our specific long-term goal is progress toward worldwide TB control and elimination, the process, connections, and products we develop will have broad application among clinical research networks in the U.S.

PROGRAM ACCOMPLISHMENTS

Overall goals: In the context of our Roadmap project mission, we have developed a detailed approach for identifying and implementing a prioritized TB research agenda, identified and addressed barriers to conducting clinical research in the public health setting, examined ways to streamline and improve the protection of human subjects, created data standards for tuberculosis and have built advanced electronic capabilities to support data collection, transfer, analysis and reporting.

Team: To achieve our Roadmap objectives we have engaged, through a truly collaborative model, over 50 public health research professionals from over 20 academic research institutions. Additionally, we have collaborated with many internationally- recognized leaders in the areas of clinical trials, tuberculosis, data systems, networks, standards development organizations and modeling. Many team members are clinicians or investigators that constitute the critical link to the public health arena. Project aims are carried out by teams comprised of members of the Tuberculosis Trials Consortium (TBTC), the Centers for Disease Control and Prevention (CDC) - specifically the Division of TB Elimination (DTBE), the Duke Clinical Research Institute (DCRI) and the many stakeholders within the TB community providing expertise and guidance on the effort.

Major milestones/accomplishments:

Engage Public Health Leaders in Clinical Research

We formed the core “Leadership” team in collaboration with TB experts. We then determined the objectives, strategy and timeline of the aim. We distributed pre-symposium thought pieces to leadership group and ultimately hosted one-day Think Tanks in 2006 and 2007 involving physicians/ scientists conducting clinical research, clinical trials experts, pharmaceutical/ industry leaders, key statisticians for global clinical trials, leadership from government, TB advocacy groups, The TB Alliance, Global experts in world-wide program implementation and the World Health Organization. Summarized findings and action plan. Disseminated findings and preparing a manuscript.

Identify and Reduce Barriers to Conducting Research at Public Health Sites

We developed metrics to evaluate success using a 8000 patient, international TBTC trial. Completed twelve site visits at US health departments serving as recruiting sites for the TBTC. We conducted focus groups at sites examining barriers to conducting research in public health clinics. Conducted data analysis from site visits, identified appropriate interventions, implemented interventions, conducted follow up for one year with sites, and conducted final data analysis. We will report findings at TBTC conference May 16, 2008.

Improve the Processes for the Protection of Human Subjects

In January 2006, we launched a "Call for Commentary" within Human Subjects Protections Community to assess current state of affairs within the human subject protection community. This goal was to access the experiences and attitudes of local Institutional Review Boards on the use of central or cooperative review mechanisms for multicenter studies.

In collaboration with the Roadmap Human Subject Protection Working Group (HSP WG) a manuscript will describe the products of the aim and we will offer a framework for considering alternative IRB review mechanisms, including key issues such as roles and responsibilities under different models, and an exploration of potential applications, strengths and concerns.

Develop advanced electronic capabilities to support data collection, transfer, analysis and reporting

The over- arching goal of the project was to address the lack of interoperability between paper-based clinical trials data collection systems, health department systems and medical records systems by creating systems that support high data quality, lower costs and improved efficiencies via electronic data management. Through collaboration with the CDC's Division of TB Elimination Data Coordinating Center, we developed a Query Tracking System and an AE/SAE Tracking Database for an 8000 patient, international trial. We conducted pilots with selected TBTC sites to test these systems. Further, we have provided web-based training and face to face training to TB Trials Consortium site personnel. The systems are fully utilized and have produced substantial efficiencies, freeing up personnel for other tasks necessary to the success of the consortium.

Website/educational tool: We launched the TB Trials Network website in 2005. Since then we developed a portfolio of educational options regarding TB specific information along with more general clinical research network educational opportunities in collaboration with the CTN Best Practices website.

Additionally, we developed the TBTC website to provide a state-of- the art method for communication and sharing of information across the 26 sites (including multiple international sites) that form the TBTC.

TB Data Standards: Through collaboration with stakeholders across the international TB community, pharmaceutical companies, statisticians, clinical data experts, and the standards community- specifically CDISC and HL7, we have defined and tested the methodology and processes for developing therapeutic area data standards. Our products include over 90 vetted data elements and more than 300 corresponding permissible values

Clinical Trials Networks (CTN) Best Practices
CTNBP

Creating, Implementing, and Sharing Best Practices for Clinical Trial Networks

Contract No. HHSN26820045218C
ADB Contract No. N01-HC-45218

Robert Harrington, MD, FACC, FSCAI

Duke Clinical Research Institute
Duke University Medical Center
Durham, North Carolina

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Robert A. Harrington, MD
Professor of Medicine
Director, Duke Clinical Research Institute (DCRI)
Link to web site of Institution: **www.dcri.duke.edu**

Robert A. Harrington, MD received his undergraduate degree in English from the College of the Holy Cross, Worcester, MA. He attended Dartmouth Medical School and received his medical degree from Tufts University School of Medicine in 1986. He was an intern, resident and the Chief Medical Resident in internal medicine at the University of Massachusetts Medical Center. He was a fellow in cardiology at Duke University Medical Center, where he received training in interventional cardiology and research training in the Duke Databank for Cardiovascular Diseases. He joined the Duke faculty in the Division of Cardiology in 1993, where he is currently a Professor of Medicine and an interventional cardiologist.

His research interests include evaluating antithrombotic therapies to treat acute ischemic heart disease and to minimize the acute complications of percutaneous coronary procedures, studying the mechanism of disease of the acute coronary syndromes, understanding the issues of risk stratification in the care of patients with acute ischemic coronary syndromes, trying to better understand and improve upon the methodology of large clinical trials. He is the recipient of an NIH Roadmap contract to investigate "best practices" among clinical trial networks.

He has authored multiple peer-reviewed manuscripts, reviews, book chapters, and editorials. He is one of the senior co-editors for the 8th edition of the American College of Chest Physicians' Consensus Panel on Antithrombotic and Thrombolytic Drugs. He is an Associate Editor of the American Heart Journal and an editorial board member for the Journal of the American College of Cardiology. He is a Fellow of the American College of Cardiology, the American Heart Association, the Society of Cardiovascular Angiography and Intervention and the American College of Chest Physicians. He currently chairs the American College of Cardiology Clinical Expert Consensus Document Task Force and the Education Strategy Committee. He chaired the 2006 Annual Scientific Sessions for the American College of Cardiology. He currently serves as a member of the FDA Cardiovascular and Renal Drugs Advisory Committee, a member of the NHLBI's study section for clinical trials and as a member of the NHLBI Working Group on Clinical Trials Methodology.

PROGRAM DESCRIPTION:

Clinical Trials Networks (CTN) Best Practices was created to:

- Foster a collaborative multinetwork of clinical research professionals, sites, and organizations.
- Improve the conduct of clinical research by defining best practices.
- Standardize information systems and other research tools.
- Engage sites in taking new research ideas quickly from concept to completion.

For more information, visit CTNBestPractices.org

PROGRAM ACCOMPLISHMENTS

Background: CTN Best Practices began in 2004 as a network of 38 U.S. hospitals specializing in cardiovascular research. Since that time, it has expanded to include several separate networks spanning research areas such as adolescent psychiatry, oncology, reproductive medicine, and tuberculosis. There were 4 Aims to the project:

Aim 1 Building and Expanding Site Capability

Implement programs and tools focused on building site capability, thereby enhancing recruitment, retention, and performance of clinical research sites.

Accomplishments

- Created CTN Best Practices Web site (ctnbestpractices.org)
    - Over 10,000 visitors to the site per month
    - International audience
    - On-line training relevant to site personnel conducting clinical research. Over 1,500 training evaluations submitted to the team to date.
    - On-line tools to assist in conducting clinical research including a list of suggested SOPs and budget templates
- Successful implementation of Study Coordinator Symposiums in conjunction with ACC 2007 and ACC 2008. Able to procure industry funding for 2008 symposium. (2008 evaluation results attached)
- Multiple posters and abstracts

Aim 2 Develop Common Data Standards

Develop a model for establishing common data elements and controlled terminology for cardiovascular disease and depression, by partnering with the Clinical Data Interchange Standards Consortium (CDISC).

Accomplishments

- Creation of Cardiovascular Domain Analysis Model
- 1st version of cardiovascular domain analyses model was distribution via CDISC for a public comment
- Active member of HL7 Clinical Interoperability Council
- Development of Clinical Content Data Standards and Methods
- Multiple publications, posters and abstracts
- Creation of on-line data standards inventory located at www.cenbestpractices.org

Aim 3 Proposal and Grant Development System

Create and implement a proposal-development system to take the best ideas for research from initial concept to execution, including preparation suitable for government, foundation, or industry funding, with a focus on encouraging public/private partnerships.

Accomplishments

The adoption and negotiation of the Rapid Start initiative which is a new way to negotiate site contracts and has been designed to address and resolve many issues surrounding the contract process. Initial results are promising with our average time from initial draft to contract execution has been reduced from 90 to 14 days. We currently have 60 Rapid Start Network agreements fully executed.

Aim 4 Network Information Infrastructure

Develop a network informatics infrastructure that can be applied across networks and provide an integrated electronic repository of tools and programs to help sites conduct studies while fostering communication across sites and networks.

Accomplishments

- Creation of site personnel libray
- Provided proof of concept with regard to technical interoperability with University of Michigan
- Creation of on-line data standards inventory located at www.cenbestpractices.org
- Creation of PRISM: an open-source application for site-based research project management
- Multiple publications, posters and abstracts

CTN Best Practices Working Committees:

Network Organization Committee: This group is composed of experienced research coordinators from both academic and private practice centers across CTN Best Practices. The group focuses on the operational aspects of conducting clinical research at the site level: identifying barriers to organizing and conducting efficient networks; tracking progress of projects at centers; soliciting, reviewing, and incorporating feedback on processes and tools; and developing implementing alternative approaches to managing, supporting, and motivating a network.

Study Coordinator Advisory Committee: This group includes 10 experienced study coordinators from among the CTN Best Practices sites. The group develops and reviews template documents, study processes, and site tools and coordinates distribution via this Web site or other means.

Steering Committee: This group includes the principal investgators of the networks that make up CTN Best Practices. This group helps set tasks and goals for the CTN Best Projects project and monitors its progress. Working closely with the Network Organization Committee, the SC offers suggestions for new tools, reviews recommended improvements, provides scientific leadership for the project, and evaluates ideas for new research projects proposed by CTN Best Practices members.

2nd Annual
Study Coordinator Symposium
Saturday, March 29, 2008 Evaluation Results

Total registrants: 96
Total registrants who attended: 68
Total registrants who did not attend: 28
Total attendees who did not register: 12
Total attendees: 80
Total attendees who completed evaluations: 66 (83%)

SUMMARY OF EVALUATION RESULTS

ROLE IN CLINICAL TRIALS
ARO/CRO: 16
Sponsor: 0
Clinical Site: 48
- Principal Investigator: 0
- Study Coordinator: 44
- Other: 4 (research director, site manager, research assistant, research administrative regulatory assistant)

Other: 2 (consultants)

RATE HOW WELL EACH PRESENTATION MET ITS OBJECTIVES.

Women and Cardiovascular Disease—Newby

State current findings in research of women and cardiovascular disease.
- Completely: 63
- Mostly: 3

Summarize future areas of focus in research of women and cardiovascular disease.
- Completely: 60
- Mostly: 6

Best Practices: Process Development—DeRaad

Identify what processes should be developed for clinical sites participating in research.
- Completely: 61
- Mostly: 5

FDA Audits—Neva

Identify ways to ensure a successful FDA audit.
- Completely: 60
- Mostly: 5

Sponsor Audits—Zimmerman
Identify ways to ensure a successful sponsor audit.
Completely: 45
Mostly: 12
Moderately: 1

RATE EACH SPEAKER'S CONTENT KNOWLEDGE.

Women & Cardiovascular Disease—Newby
Outstanding: 54
Above average: 7
Average: 2

Best Practices:
Process Development—DeRaad
Outstanding: 50
Above average: 10

FDA Audits—Neva
Outstanding: 44
Above average: 13
Average: 1

Sponsor Audits—Zimmerman
Outstanding: 30
Above average: 18
Average: 3

RATE THE SLIDE SHOW AND/OR HANDOUTS USED FOR EACH PRESENTATION.

Women & Cardiovascular Disease—Newby
Outstanding: 41
Above average: 17
Average: 5

Best Practices:
Process Development—DeRaad
Outstanding: 44
Above average: 15
Average: 2

FDA Audits—Neva
Outstanding: 40
Above average: 18
Average: 3

Sponsor Audits—Zimmerman
Outstanding: 29
Above average: 18
Average: 9

RATE THE SYMPOSIUM OVERALL.

Quality of speakers
Outstanding: 48
Above average: 14
Average: 1

Topics presented
Outstanding: 48
Above average: 12
Average: 1

Applicability of presentations to your work
Outstanding: 46
Above average: 12
Average: 4

Physical environment
Outstanding: 34
Above average: 17
Average: 9
Below average: 2

Robert Harrington, MD, FACC, FSCAI

How do you plan to use the information presented today at your clinical site?

- Apply to practice, review SOPs and CTN Best Practices.
- To improve compliance, to improve communication to IRB, improve documentation surrounding consent process.
- Certain areas discussed will be taken back to work team and may be applied to daily practices. (CTN Best Practices)
- Investigate women and CV disease trials to initiate at our site. Study tools very useful, will implement them. Will use info from women and CV disease to enroll more women patients. Excellent data points to present during screening and consenting.
- Good info. I plan on using the Web site to utilize some of the suggested logs, practice guidelines.
- I will attempt to enroll more women in our CV trials!
- Bring up at next staff meeting for all to review.
- Bring notes back to site and discuss new ideas that were brought up here.
- Visit CTNBP site and encourage colleagues to visit. Present info to fellow staff from presentation.
- Help identify site needs throughout length of study.
- Site management.
- Obtain source docs to simplify the research process.
- Very helpful and handy, especially the site tools for organization of site, FDA for possible audits very handy.
- Has considerably enlightened me re improving on process at our site.
- Change some of our practices.
- Organization!
- Work on better standardization.
- Can't wait to visit your Web site and access more info about Dr. DeRaad's topic; will use info by Neva to improve processes.
- Pass it (specific points of interest) on to co-workers at weekly meeting.
- Definitely will be using the information to "revamp" some of our current practices.
- Will visit Web site. Sounds as though there is a lot of helpful info and I have been missing out.
- Incorporate tools at my site.
- Update some of my forms.
- Will be using Web site frequently.
- Standardize procedures for all trials, i.e., forms. CYA more.
- Tons of great info! Appreciate the tools and great Web site!
- Share information with study staff. Will use some of the processes at our site.
- I plan to focus more exclusively on enrolling women in RCTs.
- CTN Web site will be utilized to obtain forms from Roger's discussion.

- Go on Web site and pulling information to better research site.
- Absolutely plan to use material, staff training, SOPs.
- Use as a resource guide for future.
- My goal is to take this information back to my office and determine how I can interject some changes to my daily work routine and create a smoother flowing generation and referencing system of data.
- We will implement some of these new strategies at our site.

If we can provide additional symposia in the future, what topics would interest you?

- Maintaining scheduled timelines. Dr. Newby's presentation was excellent but too long for time allocated.
- Regulatory work.
- Maybe a speaker who would be able to discuss the initiative of the study participant being represented as a "HERO" (ACRP & NHLBI).
- Certifications for CRC—mandated or necessary.
- Perhaps Research 101 for new research (start 1 hour prior to lunch for those needing new information).
- More like Dr. DeRaad's topic. Loved talk by Neva—great info.
- Common problems or difficulty with principal investigators (regarding communication); gaining support from other departments (techniques or practices); study coordinator time management; patient recruitment ideas.
- Tips of the trade.
- Device trials MDE-INDs/post-market studies.
- Recruiting and retaining site staff.
- Budget issues, negotiating additional costs that come up if studies go beyond plan. What to consider when creating a budget, etc.
- Source documents. Staff training.
- Nothing seems to need to be changed. This meeting was quite helpful and interesting.
- All good!
- ICF management, control or test article, document/records management best practices.

Additional Comments

- The screen was too low. Difficult to see through the heads.
- Suggest more tables/larger room setup.
- I didn't know about CTN until this meeting. I've done multiple studies through DCRI and am a member of ACRP. It would have been great to know about this at the start of the program. It seems to be a great tool.
- Appreciate the site perspective.

- I did feel that FDA audit and sponsor audit overlapped and did become a bit redundant.
- More sites to discuss their practices for research trials. Poor seating and lack of tables, speakers talk past time, and break in middle to wake up again.
- Poor seating quality. Good information, but speakers went too long and lost my interest.
- Table space for all.
- Feedback to the Hyatt: Didn't clear our table and that reduced the workspace we had for our materials.
- Selection of speakers and applicability to sites was outstanding. Thank you.
- The noise from the kitchen was very loud at my seat.
- Audit presentations could have been combined; very similar.
- 2nd Annual CTNBP Study Coordinator Symposium
  Evaluation Results
- Cathy was a great speaker! Found this to be very helpful. Both audit classes/presentations seemed redundant. (They both had good info, but a lot overlapped.) Breaks would have been helpful as I found it very difficult to listen during this entire time.
- Like the reply system!!
- Great symposium.
- Loved Dr. DeRaad's presentation!! Valuable info. Great info by Ms. Neva— good, too!
- Good info!
- Great.
- Thanks very much for lunch! Very informative! Thank you! Excellent speakers and material. Excellent information! Well-done. Excellent agenda—very good speakers. I liked the panel discussion. Excellent. Great job.
- Speakers need to be given more time. Otherwise, very informative.

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Clinical Trial Network Infrastructure & Collaborative Technology

InterTrial

HHSN-268-2004-55208-C

Stephen B. Johnson, PhD

Re-engineering clinical research in community practice

Columbia University-New York Presbyterian Hospital Clinical Trials Network
Columbia University
New York, NY

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Stephen B. Johnson, PhD
Associate Professor of Biomedical Informatics
Columbia University

Stephen B. Johnson, Ph.D. is an associate professor in Biomedical Informatics at Columbia University. He received an undergraduate degree in computer science from McGill University in 1982, and a doctorate in Computer Science from New York University in 1987. Dr. Johnson's research at Columbia began in 1988, exploring information systems that support collaboration in the biomedical domain, ranging over patient care, clinical research and basic research. Early research focused on creating online medical record systems that enable clinicians to share information during the process of patient care. Currently, Dr. Johnson directs the biomedical informatics resource for the Irving Institute at Columbia, developing a large scale system to support collaboration among investigators engaged in clinical and translational research. Dr. Johnson is also the informatics director for the Simons Foundation, where he is developing information systems to support interdisciplinary research into the etiology of autism, involving a dozen recruitment sites and multiple collaborators nationally. Key research themes that unite these projects include understanding communication patterns, workflow and the diffusion of information technology into groups to improve efficiency in these areas. A particular interest focuses on the specialized languages of science and medicine, developing computable models of these to facility interaction among humans and machines.

J. Thomas Bigger, MD (Faculty)
Professor of Medicine and of Pharmacology at Columbia University Medical Center (CUMC) and Medical Director of the Clinical Trials Network

J. Thomas Bigger, MD (Faculty) is Professor of Medicine and of Pharmacology at Columbia University Medical Center (CUMC) and Medical Director of the Clinical Trials Network, a partnership with community medical practices in New York, New Jersey, and Connecticut. Dr. Bigger has served CUMC as Director of Clinical Pharmacology, Director of the Arrhythmia Service, and as Chief of Cardiology. He was a founder of clinical cardiac electrophysiology, now a thriving subspecialty of cardiology.

Dr. Bigger's clinical research spans molecular pharmacology, integrated physiology in animal models and man, and all phases of clinical research and drug development. He has published more than 500 research papers and reviews and won the Distinguished Scientist Awards of the Heart Rhythm Society (1998) and the American College of Cardiology (2002). He has

consulted frequently for the NIH, FDA, drug and device manufacturers, and for CMS. He was a panel member for four years on the AAMC-PhRMA Working Group on Clinical Trials. In recent years he has engaged multi-disciplinary, multi-center clinical research; he was principal investigator for the Cardiac Arrhythmia Suppression Trial (arrhythmias and sudden death after myocardial infarction), The CABG Patch Trial (ICD prevention of sudden death after coronary surgery), and ACCORD's Northeastern Network (prevention of myocardial infarction, stroke, and death in type 2 diabetes mellitus). Currently, he is an investigator in NIH Roadmap's re-engineering of clinical research.

PROGRAM DESCRIPTION

Clinical Trial Network Infrastructure and Collaborative Technology (InterTrial)

Clinical research is an extremely complex process involving large numbers of stakeholders over extended time periods. Information is vital to all research activities, from conception of the protocol, through execution, to dissemination of results. Poor information flow directly contributes to lack of quality in research and high cost due to slow manual processes, introduction of errors and the inability to combine information from fragmentary or isolated sources. Unfortunately, information technology has had little penetration into the clinical research enterprise. Most of this effort has concentrated on trials in academic medical centers. The needs of investigators in community settings differ in striking ways, and are not adequately served by software provided by industry sponsors.

We have developed a successful working clinical trials network of 39 community practice research sites with centralized administration located at an academic medical center. Clinical research networks offer certain economies of scale by providing access to sufficiently large subject populations, standardizing best practices and centralizing administrative, financial, regulatory, and educational activities. However, the efficiency and expansion of the network are limited by the lack of information technology resources. The broad, long-term objectives of this proposal are to address these limitations by improving the information flow among investigators, administrators and participants.

PROGRAM ACCOMPLISHMENTS

The InterTrial Project in the Columbia University Clinical Trials Network
Stephen B Johnson, J Thomas Bigger, Rita Kukafaka

The InterTrial project explored the re-engineering of clinical research in community practice settings within the Clinical Trials Network (CTN) at Columbia University. The research employed three interconnecting approaches: implementing organization structures and processes within the network, studying stakeholder needs and work processes, and developing new software solutions for use by network staff. Findings from these efforts are summarized briefly below.

The Clinical Trials Network consists of 39 community clinical research sites in the suburban areas near New York City. A variety of organizational structures and processes were piloted in preliminary work, and tested under the present project.

Another important organizing principle is the support of a wide range of research protocols, rather than focusing on a single disease. This allows different sites to specialize in different areas, while the network benefits overall from a diversified portfolio, pursuing opportunities as they arise from federal and industrial sponsors.

The most important aspect of the organizational structure is the Research Support Hub (RSH), which coordinates all activities within the network, by conducting regular site visits, assisting with regulatory and IRB affairs and providing support through a telephone hot line. The RSH also coordinates operations with an administrative unit, which handles contracts, budgets and related financial issues. We found strong central support, regular quality assurance visits, facilitation of networking between clinical sites all contributed to improving the research enterprise. In particular, the use of special RSH "liaisons" was critically important for early detection and resolution of problems at the sites.

In additional to exploring processes at the organizational level, we also conducted a series of studies to understand workflow within community practice sites. We focused primarily on clinical research coordinators, but also collected data on related stakeholders such as principle investigators, business managers and clinical staff who were engaged in patient care activities. Data collection methods included surveys, interviews, focus groups and direct field observation. Large amounts of data were collected and analyzed within the Information Technology Implementation Framework, a heoretical framework that we adapted for applying evidence from the social science literature to understand influences on technology adoption and multiple levels.

The data confirm that clinical research coordinators carry out most of the tasks required in clinical research. They relatively little assistance from other staff at the practice site, particularly from those responsible for direct patient care tasks. The tasks that are performed most frequently are to complete and correct clinical research forms (CRFs), make patient clinical trial appointments, obtain informed consent, complete patient scales and questionnaires, affirm inclusion/exclusion criteria and register and randomize patients. We measured perceived levels of effort expended on these tasks, and the degree of satisfaction in performing them, and identified those with the largest discrepancy (those requiring high effort but rated low in satisfaction). The greatest effort–to–satisfaction gap was found in obtaining informed consent and completing and correcting CRFs.

Problems with carrying out clinical research tasks are due in part to a lack of appropriate tools to support work, but also stem from the poor design of existing tools. In the sites investigated, the majority of clinical research tasks are performed with paper-based tools or other systems that do not employ information technology. Most of the paper forms in use are not designed well, and often entail significant redundant data entry. For example, a multi-page form may require the patient identification number, site identification number, date or other details on every page of the form. Another major source of complexity is the large number of tools needed to complete a single task. For example, to identify a patient who is eligible for a trial, a coordinator typically uses a paper tool, phone and computer. The most commonly used tools to support task completion are (in order of frequency of use): paper-based forms, phone, computer-based tools and fax. Completing a given task with a single tool was seen in only 24% of all cases; two tools were used 21% of the time, three in 21% and four in 17%. The use

of multiple tools places a significant cognitive on coordinators, because input from one tool needs to be interpreted and synthesized, then fed into another tool.

Some of these problems could be reduced with typical software tools, for example reducing redundant entry on forms. However, this is a small part of a complex system that requires significant re-engineering. In fact, computer systems were often seen to add to complexity rather than reduce it, because they only perform one function and cannot bridge the different kids of communication media that are vital to workflow. There are also fundamental problems that cannot be solved with software alone. In the community practice sites studied clinical research and patient care are parallel but disconnected processes; they share patients, staff and processes, but do not exchange information efficiently. While software that bridges these two workflows would help, it cannot change an entrenched culture. Moreover, it will not be sufficient to focus only on a single stakeholder (the coordinator). The entire set of research tasks needs to be re-engineering and distributed more equitably and efficiently throughout the staff on site. This requires thinking about hierarchical vertical relationships among staff as well as collaboration among peers. Finally, none of these changes can be implemented without taking into consideration the extremely limited resources of sites (both time and money). Re-engineering needs to consider financial and human resource factors as well as those needed for conducting science.

While we were evaluating network organization and studying research workflow, we experimented with various software solutions that we thought might address some of the problems we were seeing. We began with a software tool called STEPS (Service Tracking Evaluation and Payment System), which was developed by the Clinical Trials Network prior to the project. STEPS provides a simple web-based input system for sites to enter visit dates and status on a periodic basis. This information is used to prepare payments to the sites on a quarterly basis, as well as for administrative purposes within CTN. STEPS came to be seen as an important tool that could guide research coordinator workflow, and help with the conduct and documentation of research visits and procedures. In addition, the software also facilitates making reimbursement faster and more accurate, a major incentive for sites.

As we studied research workflow, it became clear that several other functions could be provided to help coordinators. We decided to complement STEPS with a wiki platform (web pages that can be edited). This enables site staff to maintain their own wiki pages and store study related documents. In addition, we added tools to support their workflow, to manage lists of “to-do” items, and maintain simple calendars of activities. This was integrated with activities for protocols stored in the STEPS database. We developed a prototype and demonstrated to a focus group of coordinators in 2006. It was well received and we felt that the features demonstrated would be a useful part of a collaborative clinical research environment.

We then began developing a software system called WorkWeb that would incorporate all of these ideas, and deliver them within a new collaborative framework. We found a simple underlying model to support the software based on the concept of a “social network”, in which individuals are connected thought various relationships to other entities, such as departments, centers, grants, publications, trials, etc. In this model, each person (e.g. an investigator) is a “node” within the network with links to these other

entities, and each entity (e.g. a trial), in turn is modeled as a set of links to individuals (e.g. subjects enrolled in the trial). Users of this system navigate the social network to access their own activities (e.g. an upcoming visit), or to find others in the network (e.g. to collaborate on developing a new protocol). Areas of the social network be be restricted only to appropriate members, protecting information as needed (e.g. clinical trial documents).

This model turned out to be very simple, but very powerful, and we found that we could use it not only to model people and activities in the Clinical Trials Network, but also general research activities within Columbia University as part of the Clinical and Translational Science Award (CTSA). The social network can be populated from multiple data sources, such as human resource data (providing employees and their affiliations), grants (from the NIH CRISP system) and publications (from Medline). Our current network contains nodes of 3300 Columbia investigators, 165 departments (with a clinical research focus), 300 centers, 900 grants, and the publications of all the investigators involved in these organizations and activities.

We envision that the WorkWeb model can help address some of the information processing needs of the clinical research enterprise, both at the organizational level (by modeling networks and their activities directly), and by delivering tools to help with the conduct of daily tasks (scheduling, task management and site payments).

Adding HIV Resistance to a National Clinical Research Database

CNICS

HHSN268200425213C

James Kahn, MD

University of California, San Francisco
and
University of California, San Diego

BRIEFING BOOK SUMMARY

May 8, 2008

CO-PRINCIPAL INVESTIGATOR

James Kahn, MD
Professor of Medicine at UCSF
University of California, San Francisco

Dr. James Kahn is a Professor of Medicine at UCSF specializing in patient-oriented research in the areas of HIV pathogenesis, disease modeling and the development of electronic health record system applications. Dr. Kahn was an undergraduate at the University of California, Berkeley and graduated from the University of California, San Francisco School of Medicine. He received training as a medical intern and junior medical resident at Johns Hopkins Hospital, returning to UCSF to complete an internal medicine residency, a medical oncology fellowship and to participate in a medical epidemiology fellowship. Dr. Kahn joined the UCSF AIDS Program at San Francisco General Hospital in 1987. He has received a career award from the American Cancer Society and two career awards from the NIH. Dr. Kahn received one of twelve NIH "Re-engineering Clinical Research" awards from the NIH. He is also supported by the Commonwealth Fund. Dr. Kahn provided the clinical leadership for several NIH funded innovative programs including the Primary HIV Infection and Post Exposure Prevention (PEP) projects. Dr. Kahn developed an electronic medical record system, HERO (Healthcare Evaluation Record Organizer) and the linked personal health record, myHERO, for the dual purpose of providing a platform for clinical care and research. The expansion of clinical data elements and the ongoing curation and harmonization of the data elements is a focus of Dr. Kahn's scholarly activities. Working collaboratively with others, Dr. Kahn developed a mentoring program for the UCSF-Gladstone Institute of Virology and Immunology's Center for AIDS Research and the Mentor Development Program for the recently funded UCSF Clinical and Translational Science Institute. He has served on NIH review committees and has been a consultant to the Institute of Medicine, the Food and Drug Administration, the Centers for Disease Control and Prevention, and the Military Infectious Disease Research Program and served on a State of the Science panel at the NIH.

CO-INVESTIGATORS

Richard H. Haubrich, M.D.
Professor of Medicine in the Department of Medicine,
Division of Infectious Diseases, University of California, San Diego (UCSD)

Since joining the UCSD faculty in 1991, Dr. Haubrich has focused on clinical research related to antiretroviral therapy and the medical management of HIV-infected patients. In 2003, he became the overall Principal Investigator of the California Collaborative Treatment Group, a consortium of clinical investigators at five California medical schools or affiliates. Dr. Haubrich is also an active investigator AIDS Clinical Trials Group (ACTG), and is currently the Vice-Chair of the ACTG Optimization of Antiretroviral

Therapy Committee. Dr. Haubrich is Co-Director of the UCSD CFAR Clinical Investigation Core.

Dr. Haubrich has participated in numerous clinical trials that include novel antiretroviral therapies, combination antiretroviral therapy, clinical strategy trials of HIV technologies, and the utility of HIV phenotype resistance in the management of antiretroviral therapy. Dr. Haubrich's current research focuses on antiretroviral therapy for treatment-naive and treatment-experienced patients, HIV drug resistance, and pharmacology of antiretroviral agents. He is co-chair of ACTG 5142, an international, 753-patient randomized clinical trial of three therapies for treatment-naive patients and vice-chair of the ACTG OPTIONS study which will evaluate new treatment paradigms for highly antiretroviral-experienced patients. Dr. Haubrich has published extensively in peer-reviewed journals including AIDS, The Journal of Infectious Diseases, The Journal of Acquired Immune Deficiency Syndromes (JAIDS), Clinical Infectious Diseases, and Antiviral Therapy. He has been invited to present his work at numerous international meetings, including the International AIDS Conference, the Conference on Retroviruses and Opportunistic Infections, the International HIV Drug Resistance Workshop, the IAS-USA and the Infectious Diseases Society of America.

Dr. Boswell
President and CEO of the Fenway Community Health Center

Dr. Boswell has served on the Massachusetts HIV Scientific Advisory Panel, the Massachusetts Department of Public Health panel that advises the Commonwealth regarding the AIDS Drug Assistance Program (ADAP) formulary. He has been a member of the Massachusetts AIDS Design Work Group, a panel of experts that advises the Massachusetts Medicaid program regarding HIV. He has served as a member of the President's Advisory Council on HIV and AIDS since 2000. Dr. Boswell has been involved in policy development, research and training related to HIV/AIDS for approximately 20 years. For the past 5 years he has been a co-investigator of the HVTN(HIV Vaccine Trials Network) and HPTN (HIV Prevention Trials Network) networks, a group of NIH-funded sites that tested multiple approaches to preventing HIV transmission including vaccines, microbicides and behavioral interventions. Dr. Boswell serves on the Executive Committee of the Harvard Division of AIDS. In collaboration with others Dr. Boswell has contributed to the understanding of the HIV acute retroviral syndrome and long-term non-progressors; the risk of HIV transmission and medication adherence. Through a grant from the Centers for Disease Control, Dr. Boswell has helped develop a statewide network of emergency health care providers to test the concept of non-occupational post-exposure prophylaxis. He has conducted numerous clinical trials of HIV antiretrovirals including protease inhibitors, nucleoside, non-nucleoside analogues and immune modulating agents used in the treatment of HIV infection. Under Dr. Boswell's leadership, the Fenway is building a new 100,000 sq ft, $55 million building.

Simon D.W. Frost, DPhil
Associate Professor, Division of Comparative Pathology and Medicine, Department of Pathology, University of California, San Diego (UCSD)

Dr. Frost received his undergraduate degree in Natural Sciences from the University of Cambridge in 1992, and his doctorate in Zoology from the University of Oxford in 1996. He received postdoctoral training at Princeton University, the University of Oxford, the University of Edinburgh and UCSD. His research focuses on the evolution and dynamics of virus infection, particularly human immunodeficiency virus (HIV), hepatitis C virus (HCV), and influenza A virus. Dr. Frost has a long-standing interest in the evolution of antiviral drug resistance, and more recently has been investigating the pathways by which HIV escapes from neutralizing antibody responses. In addition to the work on viral evolution, Dr. Frost also has a small research program on epidemiological modeling, incorporating behavioral and biological information into network-based models of transmission of sexually transmitted infections.

Sonia Jain, PhD
Assistant Professor (Associate Professor with tenure, effective July 1, 2008) Biostatistics and Bioinformatics in the Division of Biostatistics & Bioinformatics Department of Family & Preventive Medicine,
University of California, San Diego (UCSD).

Dr. Jain joined UCSD at the end of 2002 after completing a PhD degree in Statistics at the University of Toronto in Toronto, Canada. Her primary research interests are Bayesian methods for complex data and developing statistical computing algorithms, specifically Markov chain Monte Carlo techniques. Dr. Jain's area of application is analyzing high-dimensional clinical data using both traditional analytic methods and novel methodology. Dr. Jain has more than five years of experience in the design and analysis of clinical data, including statistical genomics. Dr. Jain is currently serving as the lead Biostatistician/Bioinformatician on several NIH-funded studies in HIV, Cancer, and Glaucoma. She is the lead Biostatistician for the California Collaborative Treatment Group (CCTG), a consortium of clinical investigators at five California medical schools or affiliates. Dr. Jain serves as a member of the NIH/NCI Clinical Oncology (CONC) study section as an expert clinical Biostatistics reviewer. She also serves as the expert Biostatistician reviewer for the UCSD Cancer Center's Protocol Review and Monitoring Committee (PRMC) and Data Safety and Monitoring Board (DSMB).

Mari M. Kitahata, MD, MPH,
Associate Professor of Medicine, University of Washington.

Dr. Kitahata is Director of the Clinical Epidemiology and Health Services Research Core of the UW Center for AIDS Research (CFAR) and the PI of the UW HIV Cohort, which is a longitudinal observational study of HIV-infected patients who receive primary care in the UW Harborview Medical Center Madison HIV Clinic and the UW Medical Center Virology Clinic since 1995. She was instrumental in designing the UW web-based electronic medical record (EMR) and HIV-specific EMR components to collect standardized data for the UW HIV Cohort. She developed the UW HIV Information System (UWHIS) to integrate comprehensive demographic, clinical, laboratory, medication, and socioeconomic data on the Cohort from the UW EMR and other institutional data sources linked to biological specimens supporting significant HIV

clinical, epidemiologic, and translational research. Dr. Kitahata's research focuses on outcomes and complications of HIV treatment and includes studies of virologic, immunologic, and clinical outcomes of HAART, optimal antiretroviral management strategies for when to initiate and switch HAART, and the effect of physicians' experience with HIV disease on survival. Dr. Kitahata has ongoing collaborations in several multi-center HIV cohort studies nationally and internationally. She is the UW PI of the CFAR Network of Integrated Clinical Systems (CNICS) project examining outcomes of treatment in the HAART era among HIV clinical cohorts at CFARs throughout the U.S. She directs the development of the CNICS data repository housed at UW, which currently integrates longitudinal data dating back to 1995 for over 15,000 patients from seven CFAR-affiliated HIV cohorts around the country. Dr. Kitahata is the UW PI and directs the Data Management Core for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) project integrating data on over 90,000 patients from more than 50 sites across the US and Canada, as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) initiative.

Michael M. Lederman MD
Scott R. Inkley Professor of Medicine, Case Western Reserve University (CWRU)
Director of the CWRU Center for AIDS Research (CFAR).

Dr. Lederman has been involved in AIDS research and care since 1982 and he established the HIV clinic (the Special Immunology Unit) at CWRU/UHC in 1985. He is an experienced clinical immunologist with a major research interest in the mechanisms of immune deficiency and immune restoration in HIV infection. He has been the director of the top-ranked ACTU at Case since it was founded in 1987 and within the ACTG has served as first chairman of the Immunology Laboratory Committee, chairman of the Immunology Research Agenda Committee and the Executive Committee and Scientific Agenda Steering Committee. He now leads the ACTG Immunology Core Laboratory program. He has an international reputation as an expert in mechanisms of immune deficiency, cellular restoration and immunologic therapies in HIV disease. He is on the Scientific Advisory Board for the French Agence Nationale de Researches sur le SIDA (ANRS) and a member of the Tropical and Clinical Immunology and Infectious Diseases Funding Committee for the Wellcome Trust. He assembled the Cleveland Immunopathogenesis Consortium (CLIC) in 2004 in order to explore the pathogenesis of HIV-related immune deficiency. He is the PI of an international collaboration (AI 43645 and AI 71944) that is developing chemokine analogs as antiviral topical microbicides, and has served as project leader of another NIH-funded program (AI 55793) to develop novel adjuvants for vaccination strategies in HIV disease and has more than 230 peer-reviewed research publications.

W.C. Mathews, MD
Professor of Clinical Medicine
Director, Owen Clinic

Dr. Mathews has been a member of the UCSD medical faculty since 1979 and is currently director of the Owen Clinic and Professor of Clinical Medicine. He received his medical degree from the University of Southern California in 1975; Dr. Mathews completed his internship and residency at UCSD.

When the UCSD Medical Center and the Department of Medicine established the Owen Clinic in 1982, Dr. Mathews headed its all-volunteer medical staff that provided health care to San Diego's gay and lesbian community. As the AIDS epidemic struck San Diego, the Owen Clinic rapidly evolved as a major center for HIV care and currently serves more the 900 patients.

Since the onset of the AIDS epidemic, Dr. Mathews has served on many local, state, and national committees which address legal, political, and medical issues in HIV infection. His appointments include founding president of the San Diego Association of Human Rights, the local organization of gay and lesbian physicians, as well as memberships on the San Diego Regional Task Force on AIDS, The Ryan White Act Planning Council, the San Diego County Medical Society AIDS Committee, the State of California Attorney General's AIDS Fraud Task Force, the National Advisory Committee of the Robert Wood Johnson Foundation AIDS Health Services Program, and the American Association of Medical College's Committee on AIDS and the Academic Medical Center.

Most recently, Dr. Mathews has been intensely involved with two projects in Africa. Through a grant with Department of Defense, he has been working with military in Africa, trying to curtail HIV transmission rates. The second project has been working with HRSA, setting up HIV treatment programs under the guidelines of the Centers for Disease Control.

Richard D. Moore, MD, MHSc
Professor of Medicine, Johns Hopkins University School of Medicine.

Dr. Moore has faculty appointments in the Division of Infectious Diseases and Division of Clinical Pharmacology, and has a joint appointment in the Department of Epidemiology of the Johns Hopkins Bloomberg School of Public Health. Dr. Moore has been an HIV clinical and epidemiologic investigator since 1987 and has authored over 240 papers and book chapters. He is the Director of the Johns Hopkins Program in HIV Outcomes Research, Director of the Johns Hopkins HIV Outpatient Clinic and Principal Investigator of the Johns Hopkins HIV Clinical Cohort, a longitudinal cohort study of HIV care that was established in 1989 (R01 DA-11602). He also serves as the Principal Investigator of two multicenter studies of HIV disease progression, the North American – AIDS Cohort Collaboration on Research and Design (U01 AI069918) and the HIV Research Network (HHSA 2902006). His research interests include the natural history, therapeutic management and outcomes of HIV infection. His studies have assessed the rates and risk factors for antiretroviral drug toxicity, the effectiveness of HIV therapy on clinical progression of HIV and development of opportunistic illness, the development of non-HIV related clinical events in the HIV-infected person, and the economics of HIV infection.

Michael Saag, MD

Dr. Michael Saag received a B.S. in chemistry with honors in 1977 Tulane University and earned his medical degree from the University of Louisville. During medical school, receiving the Presley Martin Memorial Award for Excellence in Clinical Medicine. He completed his residency and infectious disease and molecular virology fellowship training at the University of Alabama at Birmingham where he completed residency training and fellowship in infectious diseases and molecular virology. During his

fellowship training, Dr. Saag made seminal discoveries in the genetic evolution of HIV *in vivo*. He evaluated isolates of virus obtained from individual patients at different periods in time and cloned and molecularly characterized these isolates to determine the degree of diversity of co-existing viral variants and to describe their evolution over time. While working with Dr. Dismukes, Dr. Saag designed and led a multi-center national AIDS clinical trial on the management of cryptococcal meningitis. During the last 6 months of his fellowship, Dr. Saag conceived the concept of a comprehensive HIV outpatient clinic dedicated to the provision of comprehensive patient care in conjunction with the conduct of high quality clinic trials, basic science, and clinical outcomes research. Within the clinic structure, he established a clinical trials unit, a data management center, and a Clinical Specimen Repository designed to support the activities of the newly established Center for AIDS Research at UAB. In essence, the clinic became a "hub" for the clinical, basic science, and behavioral science investigators within the Center by creating a dynamic interface between the patients and the investigators.

Since the establishment of the clinic, Dr. Saag has participated in many studies of antiretroviral therapy as well as novel treatments for opportunistic infections. He has published over 200 articles in peer reviewed journals, including the first description of the use of viral load in clinical practice (*Science*, 1993), the first description of the rapid dynamics of viral replication (*Nature*, 1995), the first guidelines for use of viral load in practice (*Nature* Medicine, 1996), the first proof of concept of fusion inhibition as a therapeutic option (*Nature Medicine*, 1998), and directed the 'first-in- patient' studies of 8 of the 24 antiretroviral drugs currently on the market (including indinavir, efavirenz, abacavir, and enfuvirtide). Dr. Saag has served on the Editorial Board of *AIDS Research and Human Retroviruses* and Co-Edited a textbook entitled *AIDS Therapy* (Churchill Livingston, now in its 3rd edition. He currently is on the Board of Directors of the American Board of Internal Medicine (and is Chair of the Infectious Disease Subspecialty Board), the International AIDS Society-USA, and is President-elect of the HIV Medical Association. He has twice served as a member of the HIV Disease Committee of the Medical Knowledge Self-Assessment Program for the American College of Physicians. He also serves on the NIH Office of AIDS Research Advisory Council, the HHS Guidelines Panel on Antiretroviral Therapy, and on numerous state, local, and national committees. He was elected into the American Society of Clinical Investigation in 1997. Among his other awards, Dr. Saag has received the Myrtle Wreath Award from Hadassah, was listed as one of the top ten cited HIV researchers by *Science* (1996), and has been listed as one of the *Best Doctors in America* since 1994. He received the Outstanding Medical Research Achievement Award from the AIDS Task Force of Alabama, an Excellence in Teaching Award from the Medical Association of the State of Alabama, was named a "Health Care Hero" by the Birmingham Business Journal (2003), received a Service Award from the AIDS Survival Project in Atlanta (2003), was a 2004 honoree of the Birmingham Chapter of the National Conference on Community and Justice (NCCJ), a recipient of the Birmingham Chamber of Commerce Spirit of Birmingham Award (2005), and recipient of the UAB Alumni Society Hettie Butler Terry Community Service Award (2007).

PROGRAM DESCRIPTION

The basis for the project was the CNICS network. CNICS, Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS), is a novel platform for research with approximately 17,000 patients (and expands at about 1,000 new patients per year) based upon the existing point-of-care electronic medical records at seven CFAR sponsored clinics (R24 AI067039-01A1 M. Saag PI). CNICS was created to complement randomized controlled studies and other observational studies, with a new data based upon point-of-care collection and curation of uniform data elements. The central challenges for disease management research are to develop a research agenda and innovative database that effectively and rapidly addresses the critical questions and is flexible enough to address additional questions as they arise. The CNICS group is conducting outcomes research, investigating key current clinical dilemmas in HIV therapeutics included: (1) the optimal timing and sequencing of antiretroviral therapy; (2) the evolving prevalence of viral resistance and its effects on virologic and immunologic responses, and clinical outcomes; (3) the consequences of co-infection on the natural history of HIV infection; and (4) the co-morbid complications of HIV infection. The CNICS database was flexible and built to accommodate a wider range of data, automate basic functions, improve data verification, standardize research terms, and create standards of data submission for other investigators. These activities will lead to extending CNICS to other CFAR sites and to other repositories of HIV-specific clinical data.

Many studies have evaluated the importance of HIV resistant virus in determining the virologic response (change in HIV RNA) to the next regimen after treatment failure. However, the role of resistance in predicting the progression of HIV clinical disease over a long term on continued, changing therapy guided by resistance testing has not been elucidated. Although increasing antiretroviral resistance to a regimen increases viral replication on-therapy with that regimen, the mutations that cause viral resistance have been shown to reduce viral replicative capacity. Studies indicate that the reduced replicative capacity, or “fitness”, of the resistant virus, and the residual antiviral activity of the failing regimen, slow immunodeficiency progression (based on CD4 cell decline) even on failing treatment.

The primary goal of this project is to expand the research capabilities of the existing clinical research network, the CFAR Network of Integrated Clinic Systems (CNICS). This will be accomplished by developing technical and analytic tools to import HIV resistance data directly from clinical laboratories into the electronic medical record (EMR) at the network’s clinical sites. At the clinical sites the data is used for clinical care and then transferred into the network’s central data repository. The aims for this project was to develop the standards, database, code and processes for the automatic download of viral resistance data into EMRs; to populate the research network’s central data repository and utilize analytic strategies and statistical methodology to define the effect of cumulative HIV resistance on the pace of development on disease progression.

The CNICS data system exists to receive, organize, store, retrieve and analyze securely transferred clinical data from electronic medical records at sites dedicated to HIV care and research. Many studies have evaluated antiretroviral treatment failure and the importance of HIV resistance; however the role of resistance in predicting the progression of HIV clinical disease has not been determined. In this application we

focus on adding the key new data elements of viral resistance to the CNICS research network.

To achieve this goal the application proposed four specific aims:

- Develop and implement prototype import software (electronic transfer of FASTA genotype nucleotide sequences and phenotype assays) into the CNICS database, database structure and methods that integrate HIV resistance test information (genotype, replication capacity and phenotype assays) into clinic electronic medical record systems and then upload the data into the CNICS network.
- Disseminate the system tools at sites in the CNICS research network and implement importation of resistance information and transferring data from the sites to the central CNICS database.
- To devise tools to interpret complex patterns of resistance mutations, relate mutations to predicted drug resistance and catalog and analyze HIV medication regimen data. In particular, software is needed to parse multiple antiretroviral start/stop dates into discrete regimens and to define the level of certainty of the given regimen and drug exposure period in order to best utilize the resistance test information for clinical care and research purposes.
- Test and validate the utility of these tools built to store, transfer and analyze viral resistance data in the clinical research network.

The definition and validation of tools for determining the consequences and predictors of viral resistance, as described in this project, has significant synergy with the overall research activity of the CNICS network and for clinicians caring for HIV infected persons. Tracking treatment regimen failure and resistance over time for the entire CNICS cohort will assist future drug development and clinical trial design. In addition the tools and the technology from this application are likely to influence other novel data from clinical laboratories that in the future will likely populate clinical care sites and then ultimately populate databases created within research networks. A key development from this project is the technology, rules, software and database that allows for the transfer of genomic data (viral genomic data in this specific case but certainly applicable to other genomic data too) into clinical sites' EMRs and then the download of complex genomic data from EMRs into a network database for research.

PROGRAM ACCOMPLISHMENTS

CNICS proposed four specific aims for the project:

(1) Develop and implement prototype import software (electronic transfer of FASTA genotype nucleotide sequences and phenotype assays) into the CNICS database, database structure and methods that integrate HIV resistance test information (genotype, replication capacity and phenotype assays) into clinic electronic medical record systems and then upload the data into the CNICS network.

(2) Disseminate the system tools at sites in the CNICS research network and implement importation of resistance information and transferring data from the sites to the central CNICS database.

(3) To devise tools to interpret complex patterns of resistance mutations, relate mutations to predicted drug resistance and catalog and analyze HIV medication regimen data. In particular, software is needed to parse multiple antiretroviral start/stop dates into discrete regimens and to define the level of certainty of the given regimen and drug exposure period in order to best utilize the resistance test information for clinical care and research purposes.

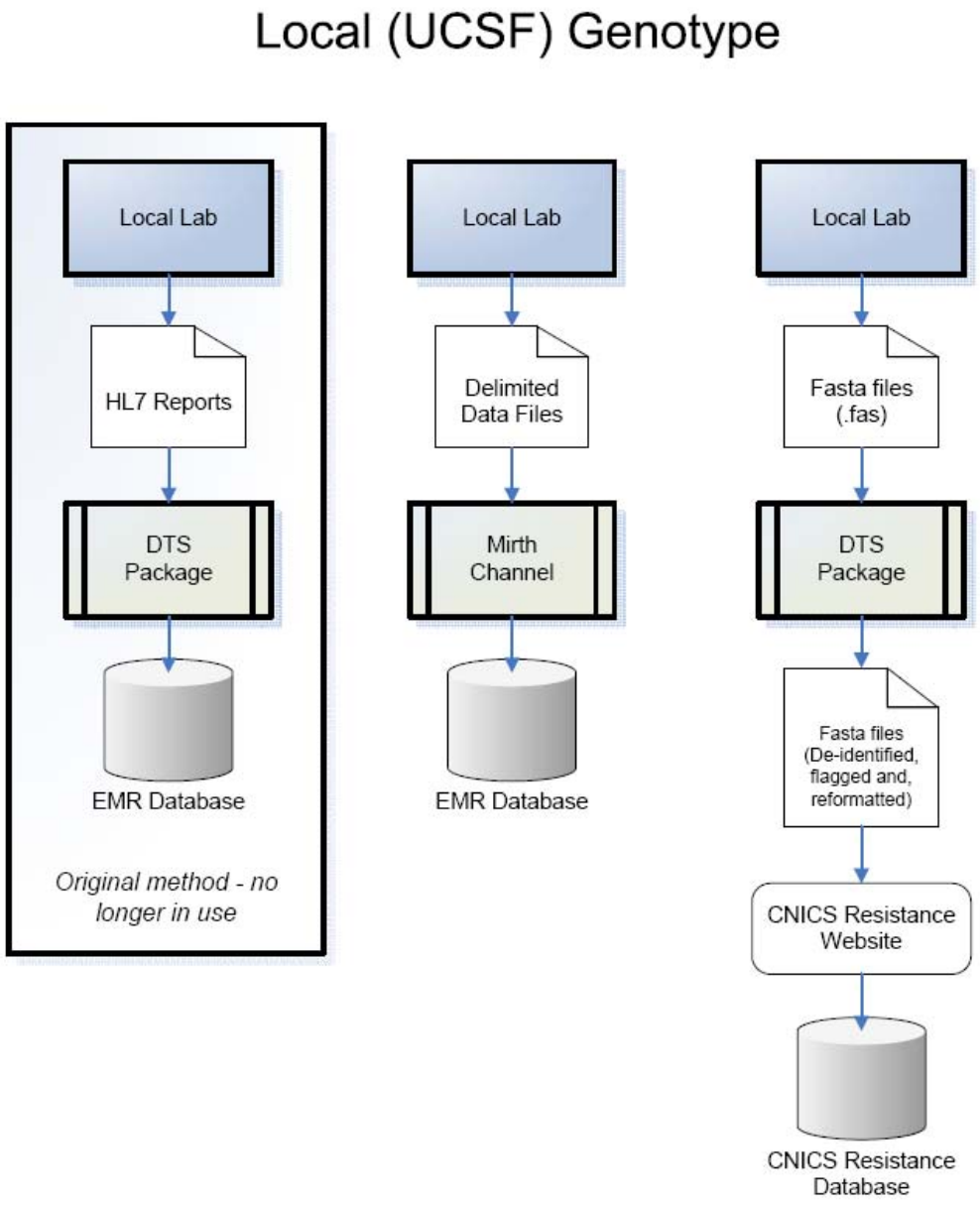
(4) Test and validate the utility of these tools built to store, transfer and analyze viral resistance data in the clinical research network.

One of the first key accomplishments was not appreciated when this project was initially proposed—the long-term survival of the research network. CNICS was a group of committed investigators leveraging center funds with established cores for clinical and translational research. CFARs were funded from multiple centers including NIAID, NIMH, NCI, NICHD, NHLBI, NID and the NIH. During this project, CNICS successfully competed for funding from NIAID (R24 AI067039-01A1 M. Saag PI). The work performed and supported under the present agreement was critical evidence that CNICS was a true network of investigators performing novel work.

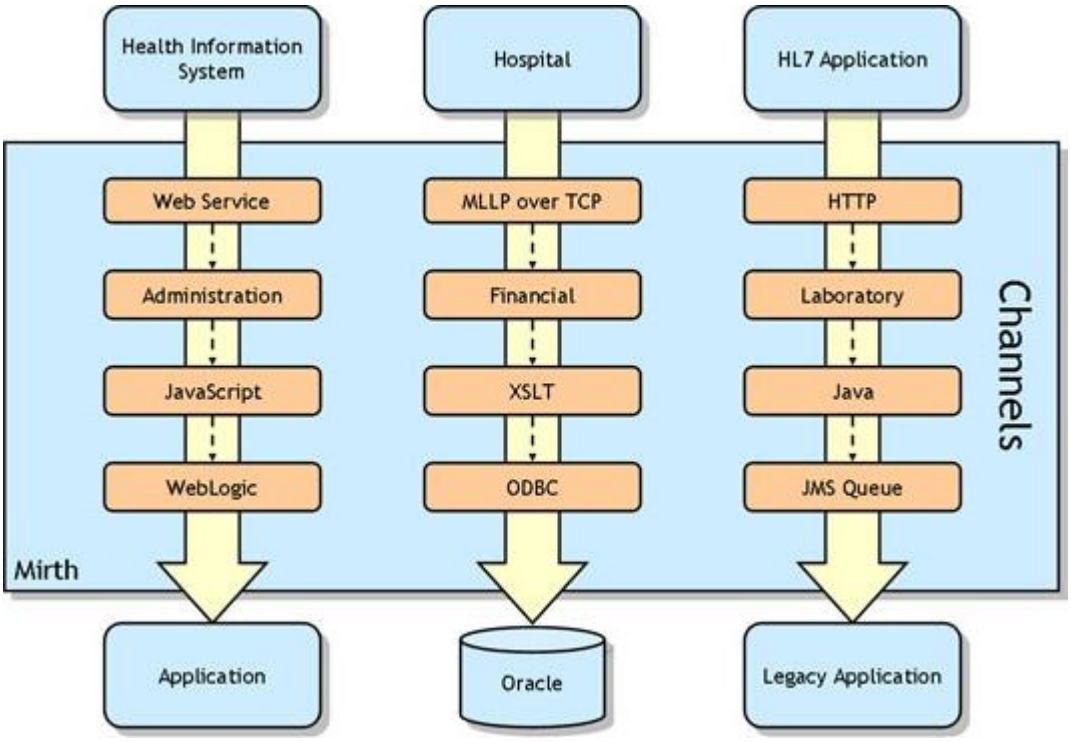
A critical aspect of the project was the acknowledgement that data regarding HIV genome, specifically the reverse transcriptase and protease genes, had three potential sources. The first source was the local Clinical Laboratory Improvement Amendments (CLIA) laboratories that provided results for clinical care. The second source was research laboratories that performed resistance tests for research studies. The third source was private or public entities that performed laboratory tests used clinically for a fee. The data that we needed was not simply the clinical result data. We were interested in the entire genome in the reverse transcriptase and protease genes. We attempted to find this solution for each source with an eye to a common pathway of populating a database for research.

The enclosed diagrams demonstrated the solutions we attempted. Some were successful and some were not. There were common issues that required attention. The three major issues faced was to develop a common pathway for each source, identify a starting point for each source and develop agreements to cooperate for each source.

The following scheme was the pathway that was attempted to generate the needed information from the local CLIA and research laboratories. The first pathway was attempted and succeeded but would not be flexible enough for each site.



We turned to Mirth which is Open Source and specifically designed for HL7 message integration, providing the necessary tools for developing, deploying, and monitoring interfaces. We used Mirth for that purpose and for non-HL7, custom delimited data files.



Mirth Utility

Filtering can be performed on incoming messages using the default message filters that are included with Mirth however we provided custom filtering scripts. Mirth's web interface made it easy to write new scripts by proving a template and editing field that allowed validation for the script code. Mirth also supports filters written in Java for complex filtering options. Transformers are used to extract the data out of HL7 messages for the application domain. Like filters, transformers can be written in several scripting languages through the web interface, or as a Java class. Incoming messages are first encoded into XML from which data can be extracted and converted to a Java object, a SQL statement, an XML file, or a variety of other types. All incoming and outgoing HL7 messages are Triple DES encrypted and stored to an internal database. Messages can be browsed from the Mirth Administrator and exported to a file. Currently supported connectors include LLP, Database, JMS, SOAP Webservices, File (network and local), PDF, FTP, SFTP. Mirth is available at no charge for an unlimited number of CPUs and channels. Mirth is also under the Mozilla Public License 1.1, which means that the source code is available and open for modification.

The Common Pathway to the resistance repository. Once a genotype sequence file and/or phenotype resistance file for each sample is available it is sent down a common pathway to the research repository database via a webpage. During upload the website validates each genotype sequence and phenotype data for header consistency. For every sequence in the FASTA file, headers are parsed and checked and header values are compared against lookup tables in the database for validity. After passing this initial validation, the nucleotide residues are counted. Genotype sequences are also checked for QA, a count of codons is performed, and the results o f a successful upload are written to the database and displayed on the website. Any errors that occur during

upload or QA are logged by the database and an error page is generated. Each upload session is given a unique identifier and each error is given a unique identifier. If errors occur, the entire uploaded file is rejected; meaning none of the data is stored by the database. The user can reference the error report via the web site, correct errors and upload again.

Genotype files require further processing, after experimenting with unmanaged and managed models, we opted for the managed model, where the genotype data is not processed until a CNICS administrator initializes the code. Genotype sequences are run against two software packages. The code first calls BLAST (http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/information3.html) to find an annotated match and identify subtype. In this step the reverse transcriptase and protease portions are compared against a library of annotated sequences obtained from Los Alamos. After this has executed successfully, the sequences are aligned against a wild type sequence (NL4-3) using HyPhy (http://www.hyphy.org). Patient sequences are broken down by into amino acids and stored as one or more amino acid per record in the database. Each record is a residue, in case of mixtures; all possible resolutions of mixtures are generated. The managed process is finalized within 48 hours of upload, after which the site can view the uploaded data and view the resulting report. All uploaded files are stored on the server, to ensure that any manipulations are traceable and comparable to the source document.

To maintain confidentiality, each CNICS site must strip any patient identifiers and replace them with CNICS identifiers. This process is facilitated by a data transformation (DTS) package, (see DTS package), that links Patient IDs to CNICS IDs automatically and constructs each sequence header to conform to the CNICS Resistance genotype header. The DTS package assigns each modified output file a standard extension. Once this step is completed, and any errors are corrected, the file is ready to be uploaded to the database via the website.

Only text formatted files with the extension '.fsc' will be accepted for upload. The extension is given to the files after being processed by the DTS package, ensuring the first level of format compatibility checking has been completed. The website renames each file using the site number and date-time stamp of upload, preserving the original name for source tracing. Tools used:

Hardware

Server	Dell Precision 530
Processor	Dual Xeon 1.0 GHz
RAM	1.0 GB

Software

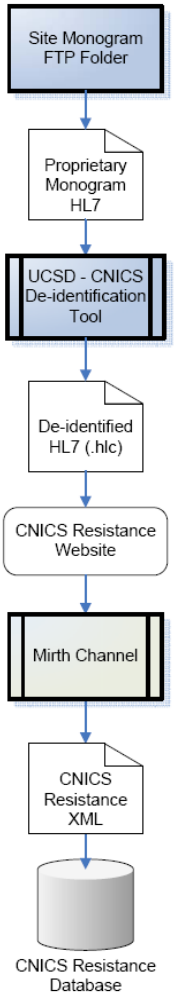
Operating System*	Windows 2000 Server
Database Server*	Microsoft SQL Server 2000
Web Server	Microsoft IIS 5.0
Firewall protection	BlackIce
Spyware protection	Adaware
	MS AntiSpyware
Development Environments	Visual Studio 2003
	ActiveState Python 2.4
Programming Languages	ASP 3.0
	Python 2.4
	Visual Basic (ActiveX)
	JavaScript
XML Tools	XMLMind XML Editor 2.10
	Oxygen XML Editor 7.0
Bioinformatics tools and libraries	BioPython 2.4
	HyPhy 0.99
	BLAST 2.2.9
Other tools and libraries	Egenix-mx-base for Python 2.4
	Visual SlickEdit 10.0
	BioEdit Sequence Alignment Editor 7.0.5
	Persits ASPUpload 3.0

The information and specifics of the database and programs can be found at: http://www.cnicsres.ucsd.edu/. There are a number of standard formats for nucleotide data. We have adopted FASTA format, as it is one of the most widespread, easily readable, and can be processed easily by a computer. The CNICS specific genotype header was designed to contain the most important identification elements for each genotype sequence. The header uses standard FASTA delimiters; i.e. header format is initialized with ">" and delimited by "|" (pipe). Phenotype data consists of IC50 (Inhibitory concentration 50%) of a wild type virus, the IC50 of the patient virus and the fold change, calculated by dividing the patient value by the wild type value. This data is provided for each drug that can be assayed, currently 17 drugs or drug combinations are assayed. Phenotype data requires text formatted files with the extension '.phc'. The extension is given to the files after being processed by the DTS package, ensuring the

first level of format compatibility checking has been completed. The upload utility checks for the appropriate header elements and parses out the IC50 values. The drug abbreviations for each IC50 value is compared against a lookup table, in the event of an unknown or new drug being assayed, the code halts the upload session and will alert the CNICS Resistance web site administrator to contact the lab and add the new drug to the lookup table.

At the same time that we completed the local and research laboratory data upload we tackled the issue of how to populate information from proprietary sources. The first group was Monogram BioSciences. The intellectual property issues were thorny and eventually eclipsed in complexity the technical issues. A more full discussion will be available in the final report, however extraordinary patience, a long term research vision, collegiality and self interest over three years eventually led to the execution of research agreements between the source of the information and the CNICS investigators. The scheme for this information is presented.

Monogram Genotype and Phenotype
(Current Method)



The data has been downloaded successfully and we are awaiting a robust and consistent download from Monogram BioSciences.

We have successfully transferred the CNICS resistance database at UCSD and merged it with the CNICS clinical database (managed at the University of Washington). We analyzed anti-retroviral regimens in a variety of ways from the CNICS clinical database and will link medication treatment patterns to the HIV resistance database.

Challenges we encountered include:

1. Identification of the original data elements. Each site that generated the data "owned" the data. Although sites were willing to share the clinical data, the more robust data that might be more interesting to the research community was more difficult to share. The part of the project that required negotiation with others was under-estimated. Despite letters of collaboration from all parties (even the proprietary collaborators) the issue of intellectual property, access to data, analysis plans, possible review requirements, process for data use, publication plans and other issues required years to work through in sufficient detail for the technical aspects to progress. In most cases this process, while daunting was successful and has led to the completion of the project. This is not universal but it has led to completion.
2. The resistance database exists at one site and the clinical database at another. As this project was first presented a single site was envisioned for both databases that would have been easier to merge data elements and tables. Projects change. During this project the databases were managed at two sites and neither site was the originally proposed site. The ability of the group to work flexibly to share database structures, elements, definitions, processes and analyses were an important and positive outcome from the project. This represented a challenge that was eventually successfully overcome.

Harmonizing NIH & Industry Sponsored Clinical Research Network Architecture

CRN Harmony

HHSN268200425217C, N01-HC-45217

J. Richard Landis, PhD

Re-Engineering the Clinical Research Enterprise:
Feasibility of Integrating and Expanding Clinical Research Networks

University of Pennsylvania
Philadelphia, PA 19104

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

J. Richard Landis, PhD
Professor of Biostatistics
University of Pennsylvania

J. Richard Landis, Professor of Biostatistics, serves as Director of the Biostatistics Unit within the Center for Clinical Epidemiology and Biostatistics (CCEB[1]), and holds a secondary appointment as Professor of Statistics in the Wharton School. Prior to assuming his current position at the University of Pennsylvania in 1997, Dr. Landis was Professor of Biostatistics at the University of Michigan School of Public Health, where he served on the faculty for thirteen years (1975-1988). In 1988, he founded the Center for Biostatistics and Epidemiology at the M.S. Hershey Medical Center of the Pennsylvania State University and served as its Director for nine years until his relocation to the University of Pennsylvania. Dr. Landis also serves as Co-Director of the Clinical Research Computing Unit (CRCU), a designated core research facility formed within the CCEB to support the conduct of multi-center clinical trials and patient-oriented clinical research projects. He is PI of two clinical research networks that have been re-funded for an additional five years (2003-2008) – the Chronic Prostatitis Clinical Research Network (CPCRN) and the Interstitial Cystitis Clinical Research Network (ICCRN), coordinated within a unifying framework as the Urological Pelvic Pain Clinical Research Network (UPPCRN[2]) . Dr. Landis also currently serves as Co-PI for the NIDDK's adult Chronic Renal Insufficiency Cohort (CRIC[3]) Research Network, with Harold I. Feldman, M.D. as PI.

For over thirty years now, Dr. Landis has been actively involved in collaborative biomedical research, and the development and evaluation of methods for the analysis of categorical data, resulting in more than 150 co-authored articles in the peer-reviewed scientific literature. Dr. Landis's publications are in the areas of statistical methods for repeated measurement and longitudinal categorical data, epidemiological studies, complex sample surveys and applications to cardiovascular, ophthalmology, respiratory, psychiatric, renal and urological research. Dr. Landis is a Fellow of the American Statistical Association, elected member of the International Statistical Institute, recipient of the Mortimer Spiegelman Gold Medal Award and recipient of an Environmental Protection Agency Scientific and Technical Achievement Award.

PROGRAM DESCRIPTION

This feasibility project creates an organizational framework (investigators, clinicians, facilities and Office of Human Research (OHR)) that contributes clinical research network re-engineering materials (standards, methodologies, and technology infrastructure) to a project framework of existing NIH and industry-sponsored Clinical

[1] http://www.cceb.upenn.edu/about/
[2] http://www.cceb.med.upenn.edu/uppcrn
[3] http://www.cceb.med.upenn.edu/cric

Research Networks (CRNs). CRNs will apply essential re-engineering materials to improve, harmonize, and integrate research operations. OHR and CCEB hold unique institutional roles at UPENN that enable them to catalyze change across multiple CRNs using novel partnerships. Results will be disseminated by the Office of Human Research to NIH, UPENN, and the public, so that standardized materials and procedures may be employed by newly emerging CRNs. This microcosm represents a scalable, prototypical, re-engineered research enterprise architecture for the conduct of clinical research within a broad-based frame work

PROGRAM ACCOMPLISHMENTS

Program: Re-Engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks

Project Goals

The Penn Roadmap program focused on improving the clinical research enterprise by adopting a systematic infrastructure that will better serve the evolving field of scientific discovery. This feasibility project created an organizational framework of investigators, clinicians, facilities and the Office of Human Research, that contributed clinical research network re-engineering materials (standards, methodologies, and technology infrastructure) to a project framework of existing NIH and industry-sponsored Clinical Research Networks (CRNs).

Project Milestones and Accomplishments

This project successfully implemented a new standards-based clinical research informatics (CRI) platform to support the conduct of clinical and translational research projects throughout the Penn School of Medicine (SOM) using the Oracle Clinical (OC) Pharmaceutical Application. To demonstrate proof of concept for these new CRI methods and tools, the Clinical Research Computing Unit (CRCU) developed and deployed pilot data management systems for six (6) clinical trials, utilizing OC tools. Moreover, these OC tools have now been applied within CRCU sponsored programs to a large-scale ophthalmology randomized clinical trial (RCT), deployed at more than 50 sites nationally.

Each of these 6 successive pilot projects, spanning varying content areas of endocrinology, infectious diseases, immunology, cardiology and hematology, required developing a series of new Case Report Forms (CRFs), utilizing Common Data Elements (CDEs) from the OC Global Library (if already present), beginning with the NCI-sponsored global library, described in (http://ncicb.nci.nih.gov/NCICB/infrastructure/cacore_overview/cadsr), developed within the cancer BioMedical Informatics Grid (caBIG) program, as well as inserting all newly developed CDEs into the Penn Medicine OC Global Library for re-use in subsequent CRFs. CDEs were developed using Clinical Data Interchange Standards Consortium (CDISC) standards for variable names and formats (http://www.cdisc.org/). Two of these projects meet FDA 21 CFR Part 11 compliant system requirements.

Progressively over time, as these CRFs were added to the global library of common data elements (CDEs), the number of new CDEs and CRFs required to develop

subsequent clinical trials in the same content area decreased substantially. In particular, nearly all CRFs (and CDEs) for the first four projects were developed as new elements; however, for the last two projects more than 50% of the CDEs were re-used from the global library. Consequently, the number of development hours needed to deploy those OC data management systems were reduced by nearly 50%.

Based on the increasing experience of the OC development team, together with the expanding number of CDEs and CRFs within the global library, the development time for new projects should continue to decline.

In addition, the program focused on refining the Oracle Adverse Event Reporting (AER) tool to align with emerging standards and routinize this process in clinical trial research networks. Installation of the Thesaurus Management System (TMS) module and other innovative modifications have been developed to enhance the AER system. This will allow us to fully utilize MedDra and concomitant medication dictionaries in the coding, evaluation, and reporting of adverse events.

A different clinical research method integration approach was required for a large-scale, diverse research network within the Penn Roadmap program. This epidemiology project is a cooperative effort between the CRCU, the University of Pennsylvania Principal Investigator, community-based physician practices and an independent Clinical Research Organization (CRO), under the direction of the Industry sponsor with guidance provided by the FDA. The CRCU worked collaboratively through the sponsor and CRO to reach recruitment, retention and data quality standard goals in the extension of this project to more than 1007 physician practices. The project has successfully enrolled 3954patients and in its' third year of follow-up has a high rate (83%) of retention.

The introduction of a Clinical Trial Management Software (CTMS) tool represents the opportunity to apply the infrastructure developed in other projects to the Chronic Renal Insufficiency Cohort (CRIC) Study as the CTMS provides methodologies that can be applied horizontally and vertically to facilitate recruitment and include new pools of potential participants from among diverse populations, as well as to propose novel patient management and treatment strategies.

During Phase 1, the CRIC Study successfully enrolled 3839 participants and is conducting the fifth year of follow up visits. The retention rate has remained steady at 94%. The CRIC Study has been extended for an additional five years. We are taking this time to examine the data collections tools and methods presently in use and to evaluate the following aspects such as 1) mapping of CRFs to CRIC Scientific Domains/Hypotheses; 2) frequency of administration - ideal vs. optimal vs. acceptable; 3) logical sequence of data flow, skip patterns, etc.; and 4) alignment with established data standards.

The CRIC Study Steering Committee has submitted a proposal to participate in the Acute Kidney Injury (AKIN) Research Study Network thereby leveraging existing tools and technology that will ultimately enhance clinical data collected within the AKI Network.

As it evolves into Phase 2, CRIC is suited to align with the NIDDK to advance the Chronic Kidney Disease (CKD) scientific research agenda on several fronts by virtue of its network development experience. With this broad foundation of knowledge and experience, Phase 2 proposes to facilitate interaction among CKD research networks

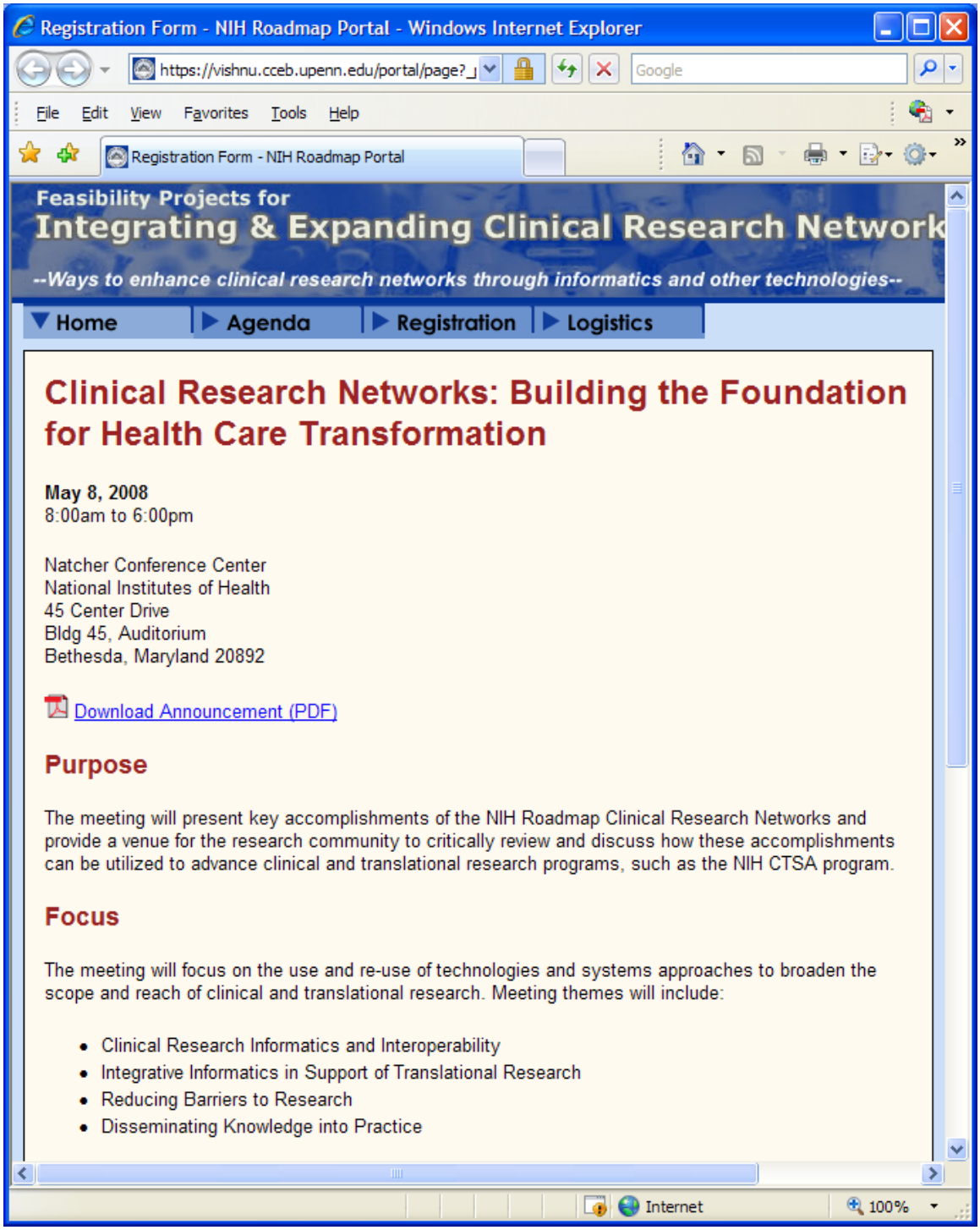
outside of CRIC (such as FAVORIT, CKiD, USRDS), thus creating a consortium of population studies, to become a core resource to harmonize CKD research.

Phase 2 will employ the best practices developed in CRIC to promote research standards in network operations, communication, governance, data collection, and information technology. The CRIC research team is experienced in expanding network participation while providing appropriate training to ensure the quality of the research resulting from this addition. In terms of direct experience, Penn has fostered network development within the NIDDK by providing the collaborative structure of the (UPPCRN) for two urology clinical trial networks to conduct joint research activities. Optimizing technology for the eventual utility of data transferred to the NIDDK Repository, the CRIC Study incorporates tools and technology that support platform-independent data standards, enabling system interoperability to promote research data sharing. The progressive adoption of these standards will ultimately be integrated internationally. CRIC in Phase 2 is also in a position to contribute to the initiatives of the National Kidney Disease Education Program (NKDEP).

In the extension of standard research materials and methods at Penn the CRCU has collaborated in several joint ventures with the Office of Human Research (OHR). The CRCU has participated in the development and presentation of a series of internal CME-certified training programs with the Office of Human Research (OHR). These programs, for investigators and research coordinators, focus on the integration of standard research tools and practices. Topics include data quality assurance and project management.

CRCU and OHR personnel have collaborated in the development of a standardized training program for monitoring clinical research at Penn. The Clinical Trials Office (CTO) of The Children's Hospital of Philadelphia (CHOP) recently joined this initiative to train research personnel across institutions, focusing on standards and techniques for managing research projects and conducting clinical research that is efficient, effective, and compliant. The development of educational content and design of key training components is in progress. Completion and intra-departmental pilot testing of the on-line training module will begin shortly.

The CRCU has served as the Roadmap Coordinating Center for all program activities, planning and coordinating eight Steering Committee meetings and providing tools and technology to enhance collaboration among the programs. The CRCU provided a suite of tools within the Oracle portal environment for Roadmap personnel as well as a public website and repository for study proceedings.


Registration Form - NIH Roadmap Portal - Windows Internet Explorer
https://vishnu.cceb.upenn.edu/portal/page?_
Google
File Edit View Favorites Tools Help
Registration Form - NIH Roadmap Portal
Feasibility Projects for
Integrating & Expanding Clinical Research Network
--Ways to enhance clinical research networks through informatics and other technologies--
Home
Agenda
Registration
Logistics
Clinical Research Networks: Building the Foundation for Health Care Transformation
May 8, 2008
8:00am to 6:00pm
Natcher Conference Center
National Institutes of Health
45 Center Drive
Bldg 45, Auditorium
Bethesda, Maryland 20892
Download Announcement (PDF)
Purpose
The meeting will present key accomplishments of the NIH Roadmap Clinical Research Networks and provide a venue for the research community to critically review and discuss how these accomplishments can be utilized to advance clinical and translational research programs, such as the NIH CTSA program.
Focus
The meeting will focus on the use and re-use of technologies and systems approaches to broaden the scope and reach of clinical and translational research. Meeting themes will include:
Clinical Research Informatics and Interoperability
Integrative Informatics in Support of Translational Research
Reducing Barriers to Research
Disseminating Knowledge into Practice
Internet
100%

HMO Research Network Coordinated Clinical Studies Network

CCSN

Contract No. HHSN 268-2004-25216-C

Eric B. Larson, MD, MPH

Center for Health Studies, Group Health Cooperative
Seattle, Washington

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Eric B. Larson, MD, MPH, MACP
Group Health Center for Health Studies
Seattle, WA

Dr. Eric Larson is Executive Director of Group Health's Center for Health Studies. A graduate of Harvard Medical School, he trained in internal medicine at Beth Israel Hospital, in Boston, completed a Robert Wood Johnson Clinical Scholars and MPH program at the University of Washington, and then served as Chief Resident of University Hospital in Seattle. He served as Medical Director of University of Washington Medical Center and Associate Dean for Clinical Affairs from l989-2002. His research spans a range of general medicine topics and has focused on aging and dementia, including a long running study of aging and cognitive change set in Group Health Cooperative - The University of Washington/Group Health Alzheimer's Disease Patient Registry/Adult Changes in Thought Study. He has served as President of the Society of General Internal Medicine, Chair of the OTA/DHHS Advisory Panel on Alzheimer's Disease and Related Disorders and was Chair of the Board of Regents (2004-05), American College of Physicians. He is an elected member of the National Academy of Sciences Institute of Medicine.

COORDINATED CLINICAL STUDIES NETWORK CO-INVESTIGATORS

Denise Boudreau, PhD
Group Health Cooperative - Seattle, WA

Dr. Boudreau, an assistant scientific investigator at Group Health Center for Health Studies and affiliate associate professor in the University of Washington's Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy is a pharmacist and health outcomes researcher. Dr. Boudreau has a master's of science in the area of pharmacy administration from the University of Rhode Island, and a PhD in pharmaceutical sciences from the University of Washington. He research interests are in pharmacoepidemiology, drug safety, cost-effectiveness analysis, validation of data sources, and the study pharmacy practice.

Paul Fishman, PhD
Group Health Cooperative - Seattle, WA

Dr. Fishman has been an Investigator at Group Health Center for Health Studies since 1996. He holds a master's degree in Economics from The American University, Washington, DC and a master's and PhD in Economics from the University of Washington. Dr. Fishman has been an affiliate professor in the University of Washington's Department of Health Services, School of Public Health and Community Medicine since 2001, as well as other teaching positions in the University of

Washington, Department of Economics and Seattle University Institute for Public Public Affairs and School of Business Administration. Dr. Fishman's research interests include the study of cost and outcomes of different organizations of primary care practices and in capitated payment reform based on a population's expected medical need.

Sarah Greene, MPH
Group Health Cooperative - Seattle, WA

Ms. Greene is a Research Associate at the Group Health Center for Health Studies in Seattle, Washington. Ms. Greene joined Group Health Center for Health Studies in 1998 as a consultant to the center's survey research program. In this role, she undertook a 360-degree evaluation of program operations and helped restructure the Program. Ms. Greene earned a bachelor's degree with distinction from Indiana University with a double major in psychology and Italian. Her master's in public health is also from Indiana University. From 1999-2003, Ms. Greene served as the Program Director for the NCI-funded Cancer Research Network (CRN) , a consortium of HMOs studying the effectiveness of cancer control interventions. Ms. Greene's areas of interest include health literacy and communication, especially for cancer prevention and control, behavior change, and applied survey methodology. Her current research is in the areas of cancer outcomes, health communications, developing tools to facilitate collaborative research, and improving the research review process.

Maggie Gunter, PhD
Lovelace Clinic Foundation - Albuquerque, NM

Dr. Gunter has been the Executive Director of the Lovelace Clinic Foundation since 1991 and Vice President of Lovelace Health Care Innovations since 1996. She holds a master's degree in sociology from West Texas State University and a PhD in sociology with a medical emphasis from the University of Pittsburgh. She is the Vice-Chair Elect of the HMO Research Network. She is actively involved in the American Medical Group Association, chairing the National Steering Committee for the Outcomes Measurement Projects and serving as a member of the Results-Based Payment System Initiative. Dr. Gunter is a current member of Lovelace Health Systems' ethics committee and past chair of the Lovelace Institutional Review Board. Since 1995 she has served on the national steering committee, Consortium Research on Indicators of Systems Performance (CRISP) project, led by Henry Ford Health System. Dr. Gunter has held past appointment as assistant Dean for Research, Grants and Endowments and assistant professor of Behavioral Medicine and Psychiatry at the Oral Roberts University School of Medicine in Tulsa, OK.

Jerry H. Gurwitz, MD
Meyers Primacy Care Institute, Fallon Community Health Plan - Worcester, MA

Dr. Gurwitz, the Executive Director of the Meyers Primary Care Institute, is a nationally recognized expert in geriatric medicine and the safe use of medications in elderly patients. He is the Dr. John Meyers Professor of Primary Care Medicine at the University of Massachusetts Medical School, where he is also chief of the Section for Health Services Research in the Division of General Medicine and Primary Care, and

Professor of Medicine and Family Medicine and Community Health. A 1983 graduate from the University of Massachusetts Medical School, Dr. Gurwitz completed his residency in internal medicine at the University of Massachusetts Hospital in 1986. He completed a fellowship in geriatric medicine at Harvard Medical School and remained on the faculty at Harvard until returning to Worcester to assume his current position as the first executive director of the Institute, in 1996. Dr. Gurwitz has published numerous original articles, reviews, commentaries and book chapters on the optimal use of drug therapy in elderly patients. He is a fellow of the American College of Physicians, the American Geriatrics Society, and the Gerontological Society of America.

Mark C. Hornbrook, PhD
Kaiser Permanente Northwest - Portland, OR

Dr. Hornbrook received a master's degree in economics from the University of Denver in 1969 and a Ph.D. in medical care organization, with emphasis in health economics, from the University of Michigan in 1975. As associate director at the CHR, he directs a team of twelve investigators along with their scientific support staff. He holds a part-time academic appointment as professor in the Population-based Nursing Department of the School of Nursing, Oregon Health Sciences University. Currently, Dr. Hornbrook chairs the Scientific Review and Evaluation Board of the Health Services Research and Development Service, Department of Veterans Affairs. He also is a member of the Measures Council of the Foundation for Accountability. He was named a Fellow in the Association for Health Services Research in 1996.

David R. Nerenz, PhD
Henry Ford Health System - Detroit, MI

Dr. Nerenz has directed both the Center for Health Services Research at Henry Ford Health System since 2005 and Outcomes Research at the Neuroscience Institute of Health Ford Hospital since 2003. He has held teaching positions at the University of Michigan, College of Human Medicine and Case Western Reserve University School of Medicine, Department of Epidemiology and Biostatistics. He received a master's degree of psychology from the University of California – San Diego in 1975 and a PhD in social psychology from the University of Wisconsin – Madison in 1979. His research focuses on health services and outcomes, disparities among racial and ethnic minority populations, and spinal disease management.

Richard Platt, MD MSc
Harvard Pilgrim Health Care - Boston, MA

Dr. Platt is a Professor and Chair of the Department of Ambulatory Care and Prevention. He is an internist trained in infectious diseases and epidemiology. He is a member of the Association of American Medical Colleges Advisory Panel on Research, the FDA Drug Safety and Risk Management Advisory Committee, and the IOM Roundtable on Evidenced Based Medicine. He has chaired the Executive Committee of the HMO Research Network, was co-chair of the Board of Scientific Counselors of the CDC's Center for Infectious Diseases, chaired the NIH study section, Epidemiology and Disease Control 2, and the CDC Office of Health Care Partnerships Steering Committee. His research focuses on developing multi-institution automated record

linkage systems for use in pharmacoepidemiology, and for population based surveillance, reporting, and control of both hospital and community acquired infections, including bioterrorism events.

Marsha A. Raebel, PharmD
Kaiser Permanente Colorado - Denver, CO

Dr. Reabel is Pharmacotherapy Research Manager in the Institute for Health Research at Kaiser Permanente Colorado and Clinical Associate Professor at the School of Pharmacy at the University of Colorado. Dr. Raebel's research is in patient safety and pharmacoepidemiology, specifically focusing on reducing medication and laboratory monitoring errors in the outpatient setting and on drug adverse event surveillance. She is a collaborating investigator in the HMO Research Network Center for Education and Research in Therapeutics (CERTs). Dr. Raebel received her PharmD from the University of Texas at Austin and the University of Texas Health Sciences Center.

James Ralston, MD MPH
Group Health Cooperative - Seattle, WA

Dr. Ralston joined Group Health in 2003 as both an internist in the health care delivery system and a health informatics investigator at the Center for Health Studies. Prior to coming to Group Health, he was an internist, hospitalist and attending physician at Virginia Mason Medical Center in Seattle, Washington for six years. Dr. Ralston holds a master's of public health and a medical degree from the University of Washington, and holds a teaching position in the Department of Health Services, School of Public Health and Community Medicine at the University of Washington. His research interests include health informatics and the care of patients with chronic medical conditions. Dr. Ralston was part of Group Health Cooperative's Working Group on Electronic Health Records, Health Informatics Strategy Team and currently serves on the Cooperative's Clinical Information Systems Oversight Committee and Patient Safety Committee. In addition he chairs the Clinical Information Systems Oversight Committee at the Center for Health Studies.

Robert Reid MD MPH PhD FACPM
Group Health Cooperative - Seattle, WA

Dr. Robert Reid is associate medical director for preventive care at Group Health and an Investigator in its Center for Health Studies. His research and administrative roles revolve around developing and testing innovations that optimize the delivery of clinical preventive services. Robert is also an affiliate assistant professor of health services at the University of Washington and an adjunct professor of health care and epidemiology at the University of British Columbia. Dr. Reid obtained his medical degree at the University of Alberta, and completed a residency in public health, and a PhD in health policy and management at the Johns Hopkins Bloomberg School of Public Health. He is a current Fellow of the American College of Preventive Medicine. Dr. Reid's research interests are in primary care organization and design and the translation of preventive care research into clinical practice.

Sharon (Cheri) J. Rolnick, PhD MPH, MA
Health Partners Research Foundation - Minneapolis, MN

Dr. Rolnick has held the position of Associate Director of Research in the HealthPartners Research Foundation since 1999 and as a Senior Research Investigator at the Foundation since 1992. She holds three advanced degrees from the University of Minnesota, Minneapolis – master's of educational administration, master's of public health focusing on epidemiology and research, and a PhD in Social and Administrative Pharmacy with a minor in epidemiology and research methods. Dr. Rolnick was the recipient of the 1996 Award for Excellence in Women's Health Research from the National Association of Women's Health Professionals. Her work has focused on mammography and Pap smear screening, as well as midlife and pregnancy related issues. Dr. Rolnick is a member of the Women's Health Task Force for the American Association of Health Plans and The Clinical Trials Task Force for the Society for the Advancement of Women's Health Research.

Carol Somkin, PhD
Kaiser Permanente Northern California - Oakland, CA

Dr. Somkin received her PhD in sociology from Columbia University. Her research has focused on the area of cancer, currently cancer screening and participation in clinical trials. She also has a special interest in intervention studies in multiethnic populations and the effect of socioeconomic status and race/ethnicity on health and health services use. Her work has addressed a variety of topics including the effectiveness of reminders to increase mammogram and Pap smear screening, the impact of socio-demographic and attitudinal barriers on various methods of cancer screening, and the effectiveness of a peer support program for women newly diagnosed with breast cancer. Dr. Somkin is a member of the Breast and Cervical Cancer Advisory Council of the California Department of Health Services and Chair of the Advisory Council's Public Education/Outreach Subcommittee.

Dennis Tolsma, MPH
Kaiser Permanente Georgia - Atlanta, GA

Dennis Tolsma's 12-year tenure with Kaiser Permanente's Georgia Region involved leading prevention, clinical quality improvement, and research activities for a 270,000-member HMO. He continues as Principal Investigator on several research grants, including Cancer Research Network dietary change trials and asthma epidemiology studies. His research interests include chronic disease, public health surveillance using managed care data, prevention and health promotion, and research ethics. Prior to joining Kaiser Permanente, Mr. Tolsma had a 31-year career at the Centers for Disease Control and Prevention, including serving as Director, Center for Health Promotion and Education (1983-1988) and Associate CDC Director for Public Health Practice (1988-1991.) He takes personal pride in having been one of the first 1000 Peace Corps Volunteers, serving in Thailand (1962-1964).

Eric B. Larson, MD, MPH

PROGRAM DESCRIPTION

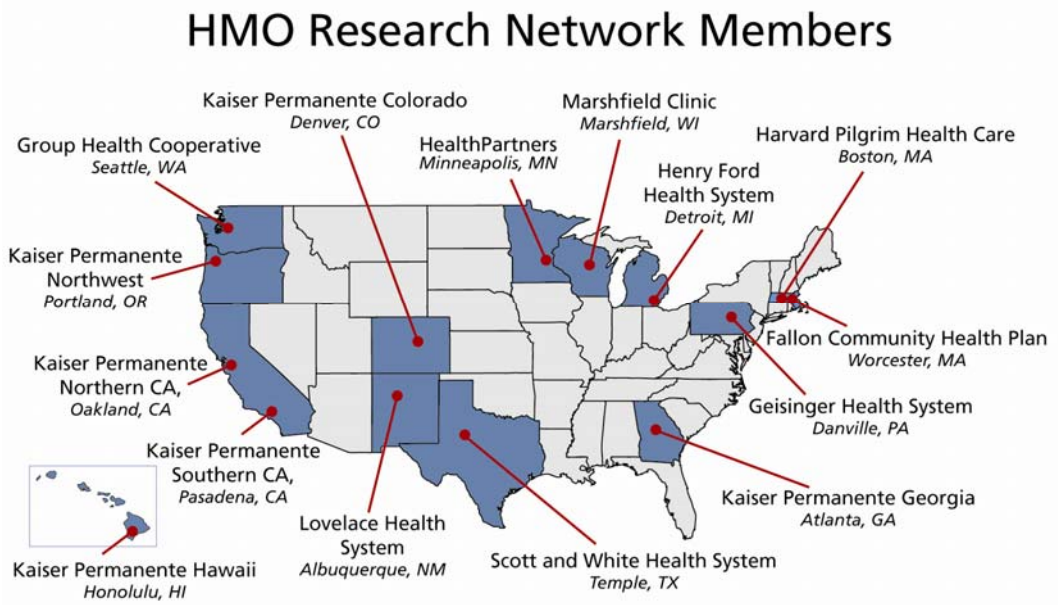
The mission of the HMO Research Network Coordinated Clinical Studies Network (CCSN) is to foster a sustainable, shared research infrastructure to enhance collaborative multi-site clinical research in order to improve health care for our health plan members, our communities and our nation. The CCSN is committed to the principles of transparency, flexibility, innovation, and discovery. The HMO Research Network is an unparalleled research facility for clinical and health services research. HMO Research Network member health plans provide comprehensive services in every U.S. region ranging from prevention to palliation, to a defined population of 13 million people or 4% of the U.S. population.

The CCSN will provide infrastructure enhancements to the HMO Research Network in the areas of project planning and development, research review, project implementation, systematized data collection and monitoring, project closeout, and dissemination. This infrastructure will dramatically increase the HMO Research Network's ability to respond to questions of national research interest, increase the pace that efficacious interventions are moved into practice, and improve research applicability across the diversity of real-world health care delivery systems.

PROGRAM ACCOMPLISHMENTS

A. BACKGROUND

The mission of the HMO Research Network Coordinated Clinical Studies Network (CCSN) was to foster a sustainable, shared research infrastructure to enhance collaborative multi-site clinical research in order to improve health care for our health plan members, our communities and our nation. The CCSN is committed to the principles of transparency, flexibility, innovation, and discovery. The HMO Research Network is an unparalleled research facility for clinical and health services research.



The largest, non-University based research network in the United States, HMO Research Network member integrated health care delivery plans provide comprehensive services in every U.S. region ranging from prevention to palliation - to a defined population of 13 million people or 4% of the U.S. population.

B. PROGRAM ACCOMPLISHMENTS

The activities of the CCSN have led to shifts in thinking and a lasting impact on the HMO Research Network, as well as comprehensive infrastructure developments.

The fact that the CCSN supported the entire breadth of multi-site research (rather than a specific content area) made this project unlike any other, past or present, conducted within the HMO Research Network. The work of the CCSN benefited collaborations, big and small, in which our 15 research centers are engaged. The contract gave us the ability to focus on challenging operational aspects of research involving multiple centers –some of which we had been trying unsuccessfully for many years to improve (e.g., IRB) – and allowed us to focus real resources toward addressing issues, build the relationships and trust needed to build bridges and facilitate inter-institutional progress. As a result of the CCSN, HMO Research Network members share greater sense of community, a more coherent common vision and stronger ties between and across sites at multiple levels. For example, we were able to capitalize on opportunities to bring IRB administrators together face-to-face to facilitate open dialogue around their own issues and concerns with alternative IRB review processes. By respecting their views and concerns while acknowledging the need for improvements, the will for change was fostered. We gained a better understanding of the complexities and intricacies of multi-site IRB review, and despite significant barriers we gained buy-in for and pilot tested a facilitated, reciprocal review process for low-risk, data only studies. Pilot tests of the facilitated process have been 100% successful, to date. The IRB group has drafted a standard operating procedure (SOP) for the new process. When considering the past 15 years of unsuccessful efforts to motivate change, we feel the changes in cross-organizational thinking and the will for change made over the past three years is remarkable.

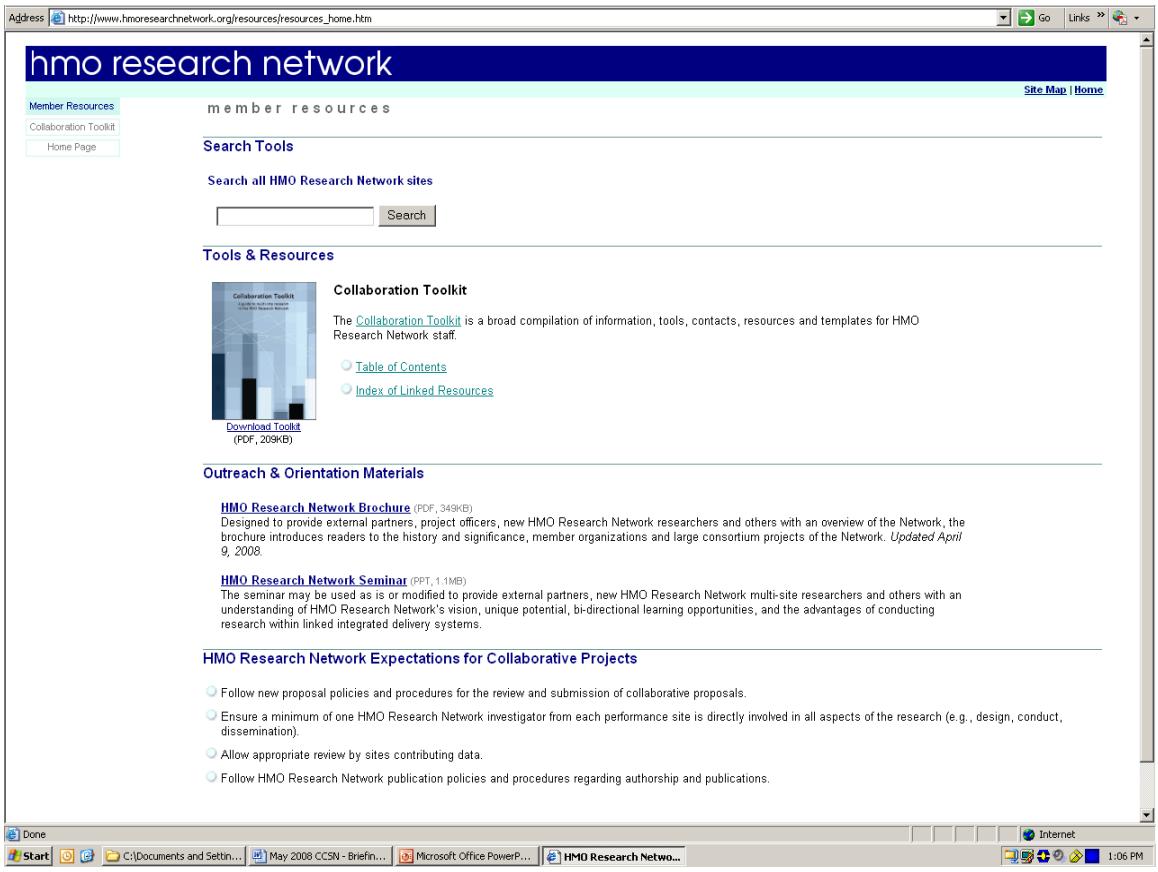
While the increased sense of community, goodwill and trust between and across sites are one part of the CCSN legacy, we also leave behind a more organized, inclusive and comprehensive organizational structure. The CCSN has provided a great deal of guidance for issues relating to multi-site HMORN assets and taken steps to ensure that such guidance will be carried on beyond the CCSN funding period. The HMORN Asset Stewardship Committee (ASC) has added to the breadth, involvement and richness of the governance provided by the HMORN; is systematically addressing a range of topics of interest to all the consortium projects; and will provide ongoing guidance for many CCSN aims – such as IRB, administrative and contractual streamlining; the Virtual Data Warehouse; data use and governance; collaborative resources; and more.

In terms of the HMO Research Network's Virtual Data Warehouse (VDW), the CCSN coupled increased philosophical buy-in with enhanced processes to contribute to the development of the VDW as a relevant and robust resource for a wider array of research topics. The CCSN developed procedures and processes for adding laboratory data to the VDW, improved documentation of and training for the use of the VDW by non-cancer related researchers, expanded availability of resources and tools to assist both

VDW programmers and a variety of investigators, and developed and is implementing a five year strategic plan for the maintenance and further development of the VDW as a Network-wide resource.

Finally, The CCSN has created many infrastructure resources to reduce barriers to multi-site trials (including administrative, operational, clinical, and more). These include the creation of more than 40 tools, forms and other resources. These are knit together with information, tips and best practices in the CCSN Collaboration Toolkit, now publically available at www.hmoresearchnetwork.org. The materials are adaptable to a range of content areas, including those in which our HMO Research Network investigators have active projects (e.g., cancer, cardiovascular, drug effectiveness, vaccine safety), and those in more formative stages, such as diabetes and aging.

This collection of resources follows the life cycle of a grant, and is geared toward the most common (but potentially challenging) aspects of multi-site studies, such as budget development, patient and provider recruitment, multi-institutional IRB review, and data use and acquisition. The lessons, tools and resources of the CCSN can be translated to other research networks and partnerships aiming to efficiently and effectively carry our multi-institutional research projects.



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C. DISSEMINATION PLAN

The lessons, tools and resources of the CCSN can be translated to other research networks and partnerships aiming to efficiently and effectively carry our multi-institutional research projects. We are drafting manuscripts summarizing the lessons learned over the course of the contract, including two relating to IRB streamlining.

The Collaboration Toolkit is being widely disseminated through the HMO Research Network, including:

- Posting www.hmoresearchnetwork.org to ensure easy access for all HMO Research Network staff, collaborators and the larger scientific community.
- CCSN listserv communications and CCSN Gazette newsletters.
- Developing, disseminating and delivering local staff and faculty seminars introducing the new web resources across the HMO Research Network.
- Developing, disseminating and delivering targeted orientations of the resources most relevant to individual work units (e.g., research operations, grants and contracts administration).
- Promoting the website at the HMO Research Network conference at the annual Board meeting, Research Administration workshop, IRB workshop, PRISM workshop, State of the Network plenary, poster sessions, and via registration packets.
- Promoting the website across the HMO Research Network by way of local communications (e.g., newsletters, intranet sites, administrative emails, staff meetings, and so on).

As part of University of Washington CTSA Community Engagement core activities, Group Health Center for Health Studies is adapting CCSN resources to new research networks in the family practice residency training program and American Indian/Alaska Native communities in Washington, Wyoming, Alaska, Montana and Idaho (WWAMI).

Reengineering Clinical Research in Critical Care
RCRCC

HHSN268200425210C; NO1-HC-45210

Alan H. Morris, MD

This is a group effort involving about 25 clinical sites and multiple investigators
IHC Health Services, Inc DBA LDS Hospital
Salt Lake City, Utah

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Alan H. Morris, MD
Professor of Medicine and
Adjunct Professor of Medical Informatics at the University of Utah
LDS Hospital

Alan H. Morris, MD is Professor of Medicine and Adjunct Professor of Medical Informatics at the University of Utah, and Director of Research and Associate Medical Director of the Pulmonary Function and Blood Gas Laboratories at the LDS Hospital. He has experience in the conduct of ARDS multi-center randomized clinical trials of treatments, including innovative therapies, for ARDS patients. He is Principal Investigator of the 4-Hospital Utah Critical Care Treatment Group (CCTG) of the NIH/NHLBI ARDS Network for clinical trials and has directed this group since 1994. This 4-Hospital group includes the LDS, Cottonwood, and McKay Dee, and Utah Valley Regional Medical Center Hospitals. He is also Principal Investigator for the NIH/NHLBI Re-engineering Clinical Research in Critical Care contract.

PROGRAM DESCRIPTION

Intensive care accounts for 20% of the total hospital health care expenditures in the US. Although the majority of care occurs in adult ICUs, pediatric critical illness is a source of significant short and long-term morbidity and care of these children consumes significant health care resources. Currently, well-designed adequately powered clinical trials are uncommon in adult and rare in pediatric critical care.

We aim to definitively evaluate the feasibility of a plan to expedite the conduct, improve the data and research quality, and increase the efficiency of ICU clinical research. To achieve this we will establish a new ICU clinical investigative strategy with currently operational integrated electronic tools (Utah Clinical Trial Toolbox) that can link different clinical research networks. This strategy will combine multiple ICUs in a large-scale clinical laboratory that should more efficiently conduct clinical ICU studies and, with the same common inter-operable electronic tools, could rapidly extend ICU research results to clinical ICU practice.

PROGRAM ACCOMPLISHMENTS

We addressed 3 specific aims in our effort to introduce computer tools for conducting holistic clinical research. We expect computer protocols to increase the signal-to-noise ratio for important clinical outcomes in clinical studies.

Aim 1: Demonstrate and Validate a new paradigm for the conduct of ICU research

We used an adequately explicit computer protocol to achieve a replicable method for blood glucose control with intravenous insulin in multiple intensive care units in hospitals

in different cultures. The computer protocol (eProtocol-insulin) enabled different intensive care units to perform in a replicable manner. eProtocol-insulin is driven by patient-specific input data and displays treatment recommendations intended to bring the patient's blood glucose within the 80-110 mg/dl target range.. This computer protocol enables the development of an extended research laboratory in which each clinical performance site replicates the behavior of other participating sites. Results from this interoperable clinical research method are thus more easily interpreted than are many clinical research results obtained with methods that vary significantly between institutions.

Aim 2: Increase the quality and efficiency of ICU clinical research

After refining and validating eProtocol-insulin, we distributed this replicable clinical research and care method for managing blood glucose to several adult and pediatric intensive care units not previously involved with the refinement of eProtocol-insulin. With this activity we tested our ability to distribute this method to naïve sites. We used eProtocol-insulin to translate research results to usual clinical practice. This computer protocol enabled 7 usual care hospitals to replicate the behavior of the research site (LDS eProtocol). eProtocol-insulin enabled translation of research results to usual clinical practice by exporting the computer protocol method to clinical practice sites.

Aim 3: Link the NIH/NHLBI Acute Respiratory Distress Syndrome (ARDS) and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Networks

eProtocol-insulin has joined adult and pediatric intensive care units in common research with a common and replicable method. It has overcome, in part, the barrier between adult and pediatric medicine. We have linked the PALISI and ARDS Networks and catalyzed collaborative research efforts. The ARDS Network is working with PALISI investigators towards a collaborative project that will join selected Pediatric ICUs to current ARDS Network centers in a randomized clinical trial of neutraceuticals. The pediatric intensivists have submitted an RO1 application to the NIH for support of this study.

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The Electronic Primary Care Research Network
ePCRN

Contract No. HHSN268200425212C

Introducing a new era in practice-based research

Kevin A. Peterson, MD, MPH

Federation of Practice Based Research Networks (FPBRN)
Leawood, Kansas

University of Minnesota
Minneapolis, Minnesota

University of Birmingham
Edgbaston, United Kingdom

University of California
San Francisco, California

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Kevin A. Peterson MD, MPH, FRCS(Ed), FAAFP
Associate Professor
Department of Family Medicine and Community Health (DFMCH),
University of Minnesota Medical School
University of Minnesota, Department of Family Medicine and Community Health

Kevin A. Peterson, MD, MPH, FRCS (Ed), FAAFP is a tenured Associate Professor in the Department of Family Medicine and Community Health (DFMCH) at the University of Minnesota Medical School and is the principal investigator for the electronic Primary Care Research Network (ePCRN). Dr. Peterson was national chairman of the Federation of Practice Based Research Network s (FPBRN) from 2001-2005 and is currently Director of the National Resource Center for Practice Based Research Networks (AHRQ). He has directed the Minnesota Academy of Family Physicians Research Network (MAFPRN), a regional practice-based research network with over 200 family physicians, for 18 years. He is the acting Director of Research in the DFMCH and acting Director for the Center of Excellence in Primary Care.

Dr. Peterson obtained his BA degree from Carleton College in Northfield, Minnesota, his MD degree from Mayo Medical School in Rochester, Minnesota, his MPH in Epidemiology from the University of Minnesota in Minneapolis, MN, and is a Fellow in the Royal College of Surgeons of Edinburgh, UK, and a Fellow in the American Academy of Family Physicians. His current research focuses on diabetes, chronic disease management, and the integration of electronic health records in practice-based research. In addition to his work on the ePCRN, he is the UMN site-Principle Investigator for the ACCORD Trial, a large diabetes clinical trial sponsored jointly by the National Heart Lung and Blood Institute (NHLBI, NIH); PI of the C3D Adopters project at the UMN Cancer Center for CaBIG (NCI), and principal investigator of a variety of clinical trials and contracts for research in practice-based settings.

CO-INVESTIGATORS

BRENDAN DELANEY, MD

Brendan Delaney is the UK lead for the ePCRN. He has been Professor of Primary Care at the University of Birmingham, UK, since 2003, prior to that he was Reader, Senior Lecturer and Research Fellow in the same department from 1993. He is an applied clinical researcher, with particular interests in the translation of diagnostic and therapeutic advances into Primary Care. Since 2000 he has led the Medical Decision Making research group at the University of Birmingham, UK, and is currently programme lead for the 'Methodology' programme of the UK NIHR National School for Primary Care Research.

He has a strong interest in methods to promote rapid and economic recruitment and data collection for primary care RCTs. Having led large primary care RCTs, the last of which was run virtually paperless, This work now supported by the NSPCR and is part of a wider collaboration around recruitment and retention to RCTs with the UK Primary Care Research Network. Brendan is also Editor in Chief of Family Practice, an international journal for academic primary care, published by Oxford University Press, and Co-director of the Birmingham Comprehensive Local Research Network (The UK equivalent of a CTSA).

STUART M. SPEEDIE, PhD

Stuart M. Speedie, Ph.D. is a Professor of Health Informatics, a Fellow in Minnesota's Institute for Health Informatics and Director of Graduate Studies in Health Informatics at the University of Minnesota Medical School. His work with the Generic Drug Branch of the Food and Drug Administration resulted in the creation of one of the earliest methods for electronic submission of information for that branch's approval process. He also lead the development of systems for the State of Maryland and others that were some the first to employ expert systems technologies to evaluate and monitor physician drug prescribing behavior. He maintains an abiding interest in the impact of health information technology on patient outcomes. Currently he is directing efforts to evaluate the utility of clinical information obtained during ambulatory encounters on decision making during emergency department visits and the impact of eprescribing and electronic health systems on the ambulatory care of patients with chronic diseases. In conjunction with these research efforts he has collaborated in the develop of an information model for primary care research (PCROM) that supports the design of systems for designing and managing research in the area.

IDA SIM, MD, PhD

Ida Sim, MD, PhD is an Associate Professor of Medicine and Director, Center for Clinical and Translational Informatics at the University of California San Francisco. She received her MD and her PhD in Medical Informatics from Stanford University, and her Primary Care Internal Medicine training from the Massachussetts General Hospital. She is also fellowship-trained in General Internal Medicine at Stanford University. Her expertise is in knowledge-based systems in medicine, clinical trial registration and reporting, evidence-based methodologies, and health services aspects of information technology use.

Dr. Sim's primary research is the design and use of clinical trial reporting systems for scientific analysis and evidence-based practice. Her current projects include the Trial Bank Project (a computable database of trial design and results), collaborations on NIH Roadmap projects on biomedical ontologies and clinical trial informatics, and a CTSA-wide project to build a repository of human studies to facilitate meta-analysis and translational knowledge discovery. In policy work, Dr. Sim was the founding Project Coordinator of the World Health Organization's International Clinical Trials Registry Platform, which sets global standards for clinical trial registration and reporting. Dr. Sim was a recipient of the United States Presidential Early Career Award in Science and Engineering in 2000, and is a Fellow of the American College of Medical Informatics.

PROGRAM DESCRIPTION

In order for the clinical research enterprise to remain successful, new partnerships with primary care providers who deliver the majority of care to the US population need to be developed. These partnerships should enhance the ability of investigators to conduct research, as well as facilitate delivery to clinicians of better tools to provide care. Randomized controlled trials (RCTs) are a fundamental tool for new discovery. Although potentially rich sources of patients and data, primary care practices have not traditionally been sites for RCTs. Reasons for this include difficulty identifying subjects, delivery of complex interventions, privacy, confidentiality, and human subjects protection issues. However, emerging technologies and methodologies can now overcome these obstacles. Introduction of open-source technology using very high speed backbone networking allows greater functionality, security, and communication, and permits the integration of primary physicians and their practice populations into the clinical research enterprise, and substantially enhances the potential for the performance of RCTs.

PROGRAM ACCOMPLISHMENTS

List and Describe the Aims of the Contract:

The electronic Primary Care Research Network (ePCRN) was initially presented in order to develop and test the feasibility of an innovative new electronic tool that could be created by applying the Internet2 “Grid” based informatics experience from several Universities with the practical experience of the Federation of Practice-Based Research Networks (FPBRN). The purpose of this software was to enhance the ability of community-based primary care medical practices to actively participate in clinical research and to promote the rapid translation of research findings into community care.

The specific objectives of the proposal were:

1. To provide a web-portal that will enable primary care practices anywhere in the United States to link with researchers in academic centers or NIH to facilitate recruitment, entry, and follow-up of multidisciplinary randomized controlled trials.
2. To establish a clinic-based registry in primary care using distributed database technology that interfaces with the web portal solution in order to enhance the process of clinical trials recruitment and the translation of research findings into practice.
3. To port a combined solution to open-source Internet-2 (Grid) components that will allow additional functionality including real-time opportunistic identification of subjects by primary care clinics, enhanced communication, additional decision support for providers, enhanced security, and warehousing of trial data emphasizing provenance and ontology of data.”

Four years later the ePCRN has exceeded the goals of the project as initially conceived. In April at the national HMO Research Network meeting, the ePCRN was introduced as “becoming both nationally and internationally as one of the most important tools available to medical practices that need access to research quality data.” Currently incorporated into community outreach programs of at least seven different CTSA centers, the ePCRN is rapidly being adopted as the premier architecture in the US for involvement of community medical practices into the academic clinical research

enterprise, and has recently completed new implementations in General Practices in England. The ePCRN has introduced a new standard for performing clinical research in primary care environments, called the Primary Care Research Object Model, or PCROM, and has developed a wide variety of research and clinical support tools designed specifically for out-patient ambulatory settings. Version 1.0 of the ePCRN software has been licensed by the Office of Business Development, and the University of Minnesota is evaluating viable economic models for sustainability. It is estimated that the ePCRN currently covers or is in the process of covering approximately one million patients in the US alone.

List and Describe the Aims Completed:

Although each seemed a giant step to us at the time, each of the specific objectives have been completed in ways that are far more successful than we had imagined.

1. A web-portal has been created that enables primary care practices anywhere in the United States to link with researchers in academic centers or NIH to facilitate recruitment, entry, and follow-up of multidisciplinary randomized controlled trials.
2. A clinic-based registry in primary care has been developed that uses distributed database technology that interfaces with the web portal solution to enhance the process of clinical trials recruitment and the translation of research findings into practice.
3. A combined solution has been ported to open-source Internet-2 (Grid) components that allow additional functionality including real-time opportunistic identification of subjects by primary care clinics, enhanced communication, additional decision support for providers, and enhanced security.

Note: Although the original application additionally envisioned “warehousing of trial data emphasizing provenance and ontology of data” at the University of California San Francisco (UCSF) Trial Bank, the World Health Organization introduced standards for Global Trial Registration during the study that led to alterations in UCSF Trial Bank plans for ontology specific data warehousing. Instead, the ePCRN has used UCSF expertise to characterize data elements by ontology and provenance using components of the Unified Medical Language System (UMLS, National Library of Medicine) extracted by the Cancer Data Structured Repository (CaDSR, National Cancer Institute). The emphasis on provenance and ontology led to the discovery of important elements that were not included in existing reference models. This led us to the development of the PCROM, a domain specific extension of the BRIDG reference model (NCI, HL7, CDISC). Trial data from the ePCRN are characterized by ontology and are warehoused at the ePCRN, or any site that is part of the virtual database.

Describe Key Accomplishments:

Perhaps much more informative than above, the following describes some of the practical effects of the successful completion of the objectives:

1. The ePCRN has produced a sophisticated “federated” Grid solution that enables and enhances T2 Translation between clinical researchers and ambulatory medical practices anywhere in the US. The ePCRN portal provides several valuable research tools that facilitate the recruitment, data collection, and follow up for multidisciplinary clinical trials. These tools shorten the time spent in

research design and implementation, greatly speed recruitment by enabling real-time opportunistic identification of subjects, enhance security, provide for the rapid collection of limited data sets with locally approved data use agreements, with informed consent can electronically populate a clinical trial management system, and provides support for many types of clinical research. The ePCRN tools facilitate the regulation and oversight of clinical research by local research network directors who are in turn responsible for providing local support and resources for community practices involved in clinical research. Additional tools facilitate IRB review, promote local population-based clinical management, and enhance clinical decision making and performance measures. In summary, the ePCRN has developed an electronic architecture that can substantially contribute to the successful re-engineering of existing models of community medical practice participation in academic clinical research.

2. The ePCRN is driven by a multiple-disease patient registry that contains a single standardized XML record for each patient seen in the practice. The registry is contained within the "ePCRN Gateway", a standardized server with "in depth" security, that remains under control of the local site administrator, while allowing Grid-based peer-to-peer interactions with other authenticated services. The local ePCRN Gateway currently interfaces with the ePCRN research portal which provides information about specific research projects as described above. But the Gateway server can also interact with other appropriately certified portals that provide support for a wide variety of services, such as disease monitoring, safety evaluations, and performance measurement. Therefore, although unanticipated, another important result of the ePCRN is the development of a standardized research "backend" that fits multiple proprietary electronic health records and that provides a standardized tool capable of providing support for multiple services provided in a Grid infrastructure across a large number of community medical practices.
3. The ePCRN has created a new primary care research object model that serves as an important link between existing reference models for clinical research and the real-world design and implementation of information systems that support the design, execution, and analysis of practice-based primary care research. This will enhance the development of future software used in the primary care environment. Implementation of these standards into computable interfaces will promote both efficiency and interoperability of clinical research findings from primary care settings.
4. The ePCRN provides a rapidly growing "virtual" database for clinical research, and provides research enhancements not envisioned, or even thought possible, before the study. This includes the ability to rapidly collect anonymous datasets across wide geographic areas, and to provide support for an economic model that reimburses local practices when the virtual database that contains their locally held data is mined for information.

Immediate Rewards and Benefits stemming from the work accomplished from this contract to: a) the Clinical Research Networks; b) Investigators; c) Research Community; the d) NIH across multiple Institutes:

a). For CRNs, the ePCRN provides valuable tools for:

- increasing the participation of community medical practices in clinical research
- increasing the speed and efficiency of subject recruitment
- testing the effect of proposed eligibility criteria on real patient populations prior to recruitment
- database searches
- rapid development of electronic case report forms
- reuse of standardized data elements and templates
- revenue sharing for regional network directors and for practices involved in clinical research
- collecting limited data sets (pending completion 9/2008)
- a new clinical trial management system designed specifically for ambulatory care sites (pending completion 9/2008)

b). For investigators, the ePCRN provides valuable tools for:

- testing the effect of proposed eligibility criteria on real patient populations prior to recruitment
- allowing targeting of specific regions, networks, or populations that contain known numbers of eligible subjects
- providing faster, cheaper, and more efficient recruiting
- enhancing the speed and reducing the cost of implementing electronic data collection. (Electronic Case Report Forms (CRFs) can be produced automatically without the expense and delay of hiring an experienced computer programmer.)
- allows research objects and templates to be stored and reused in subsequent studies
- enhancing meta-analysis
- ollowing recruitment in real time
- increasing the number of participating clinical sites

c) For the Research community, the ePCRN offers the following benefits:

- The ability to recruit for clinical studies is greatly enhanced by promoting recruitment across the general population being seen in community practices. Clinical studies will have greater likelihood of achieving full recruitment in a shorter time, costs will be reduced, and the number of potential subjects increased.
- Clinical studies will be cheaper and faster to implement with electronic data collection, instead of implementing paper forms which then require manual abstraction of data into a database for analysis.
- The use of local research network directors to support community medical providers facilitates better research in the community practice. The local director determines familiarity and training with the ePCRN software, provides access to local research resources, and enhances the transfer of relevant clinical questions back to researchers. PBRNs in primary care currently exist

in all fifty states, and their numbers are growing rapidly. The ePCRN provides a natural interface for multidisciplinary research between academic researchers and organized groups of primary care providers involved in practice-based research.

d) Patients

- Patients will have greater access to high quality clinical research.
- Opportunities for involvement in clinical research will be reviewed and approved as appropriate by the patient's regular primary care provider before being offered to the patient.

e) NIH multiple institutes:

- The ePCRN provides a method of rapidly translating NIH findings into community clinical practice. Primary care practices provide a final common pathway for the translation of information into the community for many, if not all, of the NIH Institutes and Centers. The ability to rapidly pass information regarding safety, clinical decision making, and the integration of new evidence into practice on a patient-specific level saves time and money for the primary care provider, while greatly enhancing the ability of NIH to introduce changes into community practice.
- The ePCRN technology is of value and interest to not only NIH, but is being evaluated by the CDC, FDA, AHRQ, and other government organizations interested in research quality data.

Recommendations and Best Practices For The Clinical Research Networks in moving forward

1. The involvement of community primary care practices in clinical research is both feasible and scalable.
2. Information technology is a driving force of health care change. The introduction of electronic medical records can be used to support basic network processes and enhance current capabilities.
3. It is important for successful networks to have high-level, consistent sponsor involvement.
4. Involvement of the health care community requires that providers be treated as equal partners.
5. The introduction of a single Primary Care Grid provides secure peer to peer connectivity with multiple functionalities. Like the Internet, a single grid infrastructure can support multiple functionalities and as it grows provides added value for all users.
6. Involvement of community practices requires trust and support that is best developed through local contacts. Community networks are best managed by a local research network director with expertise in practice-based research methodology.
7. Local practices should be reimbursed for mining their data.
8. Reimbursement for staff and provider time in community practices is necessary but not sufficient for successful involvement.

Internal network collaborations

Internally, the project increased the opportunity for eleven Practice-Based Research Networks to work together. This was one of the largest cooperative projects ever performed by PBRNs, with active cooperation from the following PBRNs:

1. American Academy of Family Physicians National Research Network (AAFP NRN) Director: Wilson Pace, MD
2. Alabama Practice Based Research Network (APBRN) Director: T. Michael Harrington, MD
3. Indiana Family Practice Research Network (INET) Director: Debra Allen, MD
4. USC Department of Family Medicine PBRN (LA Net) Director: Lyndee Knox, PhD
5. Minnesota Academy of Family Physicians Research Network (MAFPRN) Director: Patricia Fontaine, MD
6. Oklahoma Physicians Resource/Research Network (OKPRN) Director: Jim Mold, MD
7. Penn State Ambulatory Research Network (PSARN) Director: Alan Adelman, MD, MS
8. State Network of Colorado Ambulatory Practices & Partners (SNOCAP) Director: Wilson Pace, MD
9. South Florida Primary Care Practice-Based Research Network (SoFlaPBRN) Director: John G. Ryan, DrPH
10. South Texas Ambulatory Research Network (STARNET) Director: Walter Calmbach, MD
11. Upstate New York Practice Based Research Network (UNYNET) Director: Chet Fox, MD

Although additional cooperation with other networks was less defined, interest and cooperation included the 75 additional PBRNs from the FPBRN.

External network collaborations

During the contract the ePCRN was able to extend collaborations to include several organizations important to success of the ePCRN. Collaboration with University of California-San Francisco and University of Birmingham, England were both planned in the contract, but were external to the University of MN. New collaboration during the contract included particularly important collaboration with CaBIG (National cancer Institute), and included important collaborative work with several of the work groups including the CTMS architecture, vocabulary, security, Bridg, calendar, CaGRID, and others. In addition, work with standard development organizations including CDISC, HL7, and ASTM were facilitated and necessary. Collaboration included work with the Argonne National Laboratories and University of Chicago on the Access Grid node solutions. The national recognition of the NCRR and NIH Roadmap project made additional cooperation with foreign research organizations much easier, in particular CancerGrid (UK), eScience initiative (UK), and the Medical Record Council (UK). Additional work was performed with WONCA (World Organization of Primary Care Providers),and the North American Primary Care Research Group. Finally, additional government organizations have become involved. In particular, the AHRQ has funded a National PBRN Resource Center from two of the Roadmap projects (ePCRN, and

IECRN). This may serve as a resource for further adoption and distribution of the ideas and software developed for the creation of a national research network in primary care.

Community interactions and in reaching underserved populations

The ePCRN is particularly suited for involvement of medical practices serving rural and underserved areas. As a result, the University of Minnesota is investigating the role of the ePCRN is serving rural Minnesota practices, and in practices located in underserved areas of Minnesota. We are also collaborating with North Dakota State University and the University of North Dakota in evaluating the role of the ePCRN in helping to promote better communication and collaboration in remote sites.

The ePCRN has been instrumental in creating standardized exports from the VA Vista open source electronic health record, (WorldVista), which is expected to provide added attraction for providing academic support for rural and underserved clinics. Throughout the country, several groups in underserved areas have begun implementing the ePCRN, including a group of 14 community clinics in southern Florida (Health Care Network, Dade County), several small practices in Texas, rural sites in Oklahoma, and is under consideration at underserved Hispanic clinics in Los Angeles. Although installation is still incomplete at this time, the interest in adopting the ePCRN as a less expensive solution for providing quality and performance measures is especially appealing to small practices not generally targeted by large medical software companies.

Finally, we have just begun our first clinical trial of diabetes and peripheral vascular disease with the UMN Office of Health Disparities in an underserved urban area of Minneapolis. This should help to define barriers to care, and help to identify solutions that are more appropriate and generalizable to these communities at risk because they have been developed with the direct involvement of medical practices within the communities.

Training of personnel involved in clinical research

The ePCRN has trained Research Directors from the eleven participating PBRNs in the use of the ePCRN clinical research tools. They in turn have trained researchers in each of their regions. To date, we have authenticated and trained over 260 primary care physicians in the use of the ePCRN, and have provided unique identification and security devices to each. We have provided additional training in the use of the ePCRN tools with staff members from the participating PBRNs, and will continue to instruct in the use of the software as it is made available to more research sites.

The overall impact on the training of personnel in clinical research will take additional time to be appreciated. As the ePCRN becomes more widely adopted as a tool that facilitates translation between primary care providers and clinical researchers, the number of primary care providers willing to be involved with clinical research is likely to increase. The Future of Family Medicine project was sponsored by seven professional organizations to determine goals for securing the future of Family Medicine. One of the final goals states:“Participation in the generation of new knowledge will be integral to the activities of all Family Physicians and will be incorporated into Family Medicine training. Practice-based research will be integrated into the values, structures, and processes of Family Medicine practices.”

As practice-based research continues to grow in primary care, facilitated by tools like the ePCRN, the number of providers incorporating clinical research training into community practice will inevitably increase.

Collaborate with other funded NIH NECTAR Roadmap Contractors

The important collaboration of the ePCRN with several of the work groups from CaBIG and the National Cancer Institute (NCI) was described previously. This collaboration was essential for completing the extent of infrastructure development that the ePCRN was able to achieve. The ePCRN is currently supporting a clinical trial in Minnesota sponsored by the National Institute for Diabetes and Digestive and Kidney diseases (NIDDK) and one in Pennsylvania sponsored by NCI. We have addressed issues in vocabulary and data element development with NIDDK and the National Heart Lung and Blood Institute (NHLBI), and are using resources developed by the ePCRN to provide NHLBI with a more accurate power analysis for a proposed group-randomized study. Of course the ePCRN forms an essential part of the infrastructure for the Agency for Health Research and Quality (AHRQ) PBRN National Resource Center. We have been asked to assist with community engagement and translation of research findings into primary care practices by several Clinical Translational Science Award (CTSA) recipients from the National Center for Research Resources (NCRR). We are working closely with several Veterans Administration (VA) hospitals on VA Vista, and are working with the Center for Disease Control and Prevention (CDC) on construction of an ePCRN portal for disease specific monitoring. We are also investigating the use of the ePCRN in the creation of a Sentinel Network with the Federal Drug Administration (FDA). The ePCRN infrastructure could be used to support clinical research for any institute or center that seeks to develop better partnerships with community primary care physicians.

"Tools" as Deliverables accomplished

1. The ePCRN Gateway –(University of Minnesota license. Contact Kevin A. Peterson) The Gateway consists of a Globus Server that communicates with the ePCRN client located at the ePCRN Research Portal. The Gateway provides multiple functionalities based upon a standardized multiple-disease registry. It provides automatic registration of clinical practices, PKI security, and provides locally controlled filters for limiting searches. The gateway supports the import of Continuity of Care Record XML strings (CCR), with local opt-out facilities available. The Gateway allows local identification of patients that matches eligibility criteria passed out from the ePCRN Research Portal, and supports print, email, and text messaging to facilitate local provider contact with local patients. In addition, a second set of functionalities can be turned off or on. These include population-based disease management software for evaluation of standardized performance measures, a tool for the creation of new population based queries, an interface for data entry or correction, and advanced clinical decision support software for diabetes. Additional disease specific support modules are pending.
2. ePCRN Research Portals –(University of Minnesota license. Contact Kevin A. Peterson). The ePCRN research portal is a set of functionalities that act as a Globus Client and can interact with ePCRN Gateways in a number of ways. Although more complex to set up, ePCRN Research Portals provide researchers with an access site and the ability to pass queries out to participating clinics in real time. Portals see the

clinic Gateways as a single large virtual database. The Portals can be tailored to focus on specific functionalities of interest, such as safety monitoring, performance, or clinical trial eligibility and recruitment. Researchers can interact with specific clinical data sets from participating practices through regional Research Networks. The Research Networks oversee, direct, and electronically authorize queries and recruitment from the practices in their network.

3. ePRISM – An electronic representation of the PRISM tool for standardizing readability of patient consent forms. The tool allows capture and reuse of specific elements from consent forms as included in the PRISM handout. The tool provides for entry and storage of new consent forms, and allows new consents forms to be shared or stored privately for future use.

Describe how the results of the project will be disseminated

The organization overseeing the ePCRN is the Federation of Practice Based Research Networks (FPBRN) a national organization representing primary care PBRNs. The ePCRN software will continue to be offered through the FPBRN to its members. Several PBRN members have become part of local CTSAs, and implementation of ePCRN software is currently referred to by at least seven CTSA consortiums.

The ePCRN and the IECRN have formed the AHRQ National PBRN Resource Center. The ePCRN software can also be supplied through this National Resource Center to PBRNs who request it. The Resource Center has limited funds for assistance with installation.

The ePCRN is currently installing the ePCRN software in ten sites, including the University of Colorado and several practices in Texas through DartNet. Dartnet is an AHRQ funded contract that uses the ePCRN to perform initial evaluation of medication safety, and provides for some programming to extend the functionalities of the ePCRN.

The University of Minnesota Office Of Business Development has licensed the ePCRN software, and is evaluating additional sustainable business models for continued support and distribution of the ePCRN.

Developing a Collaborative Effort Between the Pediatric Blood and Marrow Transplant Consortium (PBMTC) and the Children's Oncology Group (COG)

COG

HHSN268200425220C

Greg Reaman, MD

COG/PBMTC Group Operations Center

Arcadia, CA

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Gregory H. Reaman, MD
Chairman
Children's Oncology Group

Gregory H. Reaman, M.D., is the first Group Chair of the Children's Oncology Group (COG). The COG was formed in March, 2000 by the merger of four legacy pediatric cancer research organizations and is comprised of over 230 member institutions, responsible for the treatment of 90% of children with cancer in North America.

Dr. Reaman is a professor of pediatrics at The George Washington University School of Medicine and Health Sciences and a member of the division of Hematology-Oncology at the Children's National Medical Center in Washington, D.C., which he directed for 17 years. Dr. Reaman is a graduate of Loyola University Chicago-Stritch School of Medicine, and completed his pediatrics training at McGill University/The Montreal Children's Hospital. His post graduate training in oncology was obtained at The Pediatric Oncology Branch of the National Cancer Institute where he served as an Investigator prior to coming to Children's Hospital, and where he continues as a Consultant.

Dr. Reaman serves or has served on the Editorial Boards of Leukemia, Journal of Clinical Oncology, Journal of Pediatric Hematology/Oncology, Pediatric Blood and Cancer, The Oncologist, Cancer, and Physicians Data Query (PDQ), National Cancer Institute as well as **www.PLWC.org** (People Living with Cancer). He has served as an Associate Editor of Cancer and currently serves as Associate Editor of Leukemia and Lymphoma. He holds the position as the Executive Vice-President for Medical and Scientific Affairs for the National Childhood Cancer Foundation (NCCF) and is a member of its Board of Trustees. Previously, he served on the Board of Directors of the American Cancer Society and chaired its Task Force on Children and Cancer.

In addition, Dr. Reaman serves on the Board of Directors of the American Society of Clinical Oncology's (ASCO) Patient Education Committee and the Educational Program Committee, and is the Chair of the ASCO Membership Committee. He is a member of the Alliance for Childhood Cancer, a member of the Data Safety Monitoring Board of the National Cancer Institute's Clinical Oncology Program, and was a member of the Food and Drug Administration's Oncologic Drugs Advisory Committee. He currently chairs its Pediatric Subcommittee. He is the author of more than 200 peer-reviewed manuscripts.

Greg Reaman, MD

COG-PBMTC CO-INVESTIGATORS

Donna Wall, MD
Texas Transplant Institute
Pediatric Blood & Marrow Transplant Program
San Antonio, TX

Kirk Schultz, MD
British Columbia Children's Hospital
Pediatric Oncology/Hematology/BMT Program
Vancouver, British Columbia Canada

John Levine, MD
C.S. Mott Children's Hospital
Department of Pediatrics and Communicable Diseases
Ann Arbor, MI

Stephen Grupp, MD, PhD
Children's Hospital of Philadelphia
Stem Cell Laboratory
Philadelphia, PA

Gregory Yanik, MD
C.S. Mott Children's Hospital
Department of Pediatrics and Communicable Diseases
Ann Arbor, MI

Michael Pulsipher, MD
Primary Children's Medical Center
Pediatric Blood and Marrow Transplantation
Salt Lake City, UT

James Lynch, PhD
University of Nebraska Medical Center
Children's Oncology Group Statistics & Data Center
Omaha, ME

Bryan Langholz, PhD
University of Southern California
Children's Oncology Group Statistics & Data Center
Los Angeles, CA

PROGRAM DESCRIPTION

The broad, long-term objective is to develop a collaborative effort between two clinical trials networks, the Pediatric Blood and Marrow Transplant Consortium (PBMTC) and the Children's Oncology Group (COG), in order to enhance the availability, safety, and efficacy of Pediatric blood and marrow transplantation performed by the PBMTC and COG, jointly optimize BMT protocol performance by the PBMTC and cancer treatment by the COG, and to advance the science and application of BMT through coordinated development of research concepts and collection of data between the PBMTC, the COG, and related networks in BMT.

PROGRAM ACCOMPLISHMENTS

The broad long term objective of this contract was to develop a collaborative effort between two clinical trials networks, the Pediatric Blood and Marrow Transplant Consortium (PBMTC) and the Children's Oncology Group (COG), in order to enhance the availability, safety and efficacy of pediatric blood and marrow transplantation performed by the PBMTC and COG. It also sought to jointly optimize BMT protocol performance by the PBMTC and cancer treatment by the COG, and to advance the science and application of BMT through coordinated development of research concepts and collection of data between the PBMTC, COG and related networks in BMT. Overall accomplishments include:

- Creation of over 220 caDSR compliant Common Data Elements (CDEs) specific to Pediatric Bone Marrow Transplantation for 3 trials developed through this initiative.
- Completion of the Common Data Element Development Joint Task Force Project between COG/PBMTC and the BMT CTN/CIBMTR/ NMDP/EMMES. EMMES will now curate the forms and questions, to create caDSR compliant common data elements and template modules, for use in Adult BMT.
- Initiation and implementation of the PBMTC organizational restructuring. Oncology-related programs will become the responsibility of the COG, and the PBMTC will enhance transplant-related and metabolic disease issues along with increased efforts in orphan diseases.
- Integration of Roadmap Network Model into the PBMTC organization: Creation and adoption of organization By-Laws, creation of a Data Safety Monitoring Committee (DSMC), re-structure of leadership organization and maintenance of a public and members-only web site.
- Creation of a Web Site Committee by PBMTC, to assume design & development efforts currently underway for both a public and member use web site. The public/private web site is anticipated to activate early May 2008.
- The three clinical trials developed through this collaboration were activated during the contract period, and the respective study committees continue to provide oversight of the studies in order to meet accrual goals.
    - Project Study #1, ASCT0431/ONC051 (SirolimusTrial), which was activated March 19, 2007 is now open at 44 institutions.
    - Project Study #2, ASCT0521/SUP051 (Etanercept Trial) which was activated April 17, 2006, is now open at 46 institutions.
    - Project Study #3, ASCT0631/SCT051 (G-CSF Primed), which was activated December 31, 2007 is now open at 9 institutions.
- Continuation of collaborative Inter-group effort between the Bone Marrow Transplant Clinical Trials Network and COG. Study BMT CTN 0501: A Multi-center, open label, randomized trial comparing single versus double umbilical cord blood transplantation in pediatric patients with leukemia and myelodysplasia, has been made available to COG BMT Centers to ensure adequate accrual to this Phase III trial. The COG/PBMTC network is currently supporting this BMT CTN research effort, and accrual is exceeding projection.
- PBMTC began development of an unrelated donor transplant study in collaboration with the Thalassemia Clinical Trials Network (TCTN) which will be supported by and conducted utilizing the PBMTC/COG clinical trials infrastructure.
- Expansion of the PBMTC network to 89 Centers and membership is expected to increase.
- Development of Standard Operating Procedures (SOPs) is underway to define the policies and procedures necessary to the operation of the PBMTC.
- Development of an affiliation agreement for a long-term working relationship between the PBMTC and COG is in progress.

Greg Reaman, MD

BUILDING COLLABORATION FOR CLINICAL RESEARCH NETWORKS

The specific aims of this contract are as follows:

1. Expanding COG's clinical trials infrastructure to enable an inter-operable clinical research network in pediatric BMT in conjunction with PBMTC.
2. Evaluating the performance of the infrastructure and inter-network informatics applications in actual inter-group clinical trials.
3. Developing standardized informatics tools that will allow for optimal data sharing of clinical research data from clinical trials between the COG/PBMTC and other networks.
4. Optimizing the COG/PBMTC clinical trials network structure as a model for performance of trials on rare and orphan disorders.

Through BAA contract, the COG staff's experience and expertise was utilized to train a small team, including a project manager and study coordinator to support the development of PBMTC studies, and expanded the scope of the existing COG electronic Enhanced Remote Data Entry System (eRDES) and database management systems to encompass the PBMTC, using flexible, user-friendly tools to accommodate their requirements for study conduct. The strength of this approach is being evaluated with the conduct of three demonstration studies. In addition to developing standardized informatics tools that can be used by both COG and PBMTC, we are now exploring collaborative efforts with other BMT-related networks to develop, conduct and share data from clinical trials. PBMTC staff are now able to use the COG eRDES study builder to rapidly design and implement data entry screens, and are able to define new common data elements using the specifications learned during this project, without assistance from a programmer.

One of the long range goals of the clinical research component of the NIH Roadmap is to foster clinical research networks that are based on common or inter-operable infrastructure elements and that conduct research both in academic and clinical care settings. This project demonstrates that by integrating and expanding clinical research networks, we broaden the kinds of research questions that can be addressed and enhance the efficiency of conducting clinical research. By expanding the COG network to assist the PBMTC in conducting their trials more rigorously and more efficiently, these two networks have demonstrated that this goal can be achieved.

Over the course of this contract, the PBMTC has undertaken numerous changes to improve network infrastructure, expand its membership and institute new policies and procedures based on the COG model, or paradigm, of network inter-operability.

- PBMTC has created new project management tools/templates for clinical trials development.
- NCCF/COG has created new efficiencies in the contracts and grants management process for the COG and PBMTC networks.
- PBMTC is currently exploring collaborative efforts with the Thalassemia network and with organizations focusing on Sickle Cell Disease.

- PBMTC is improving lines of communication within the network, while simultaneously expanding the network membership.
- PBMTC is seeking broader input and participation from the PBMTC network membership: in study development, participation in planning and conducting future Group meetings and in the planning and conduct of BMT scientific symposia.

As we near the end of this project, PBMTC can now demonstrate the success of the infrastructure developed during this project, with the conduct of their PBMTC-initiated studies, as well as with those studies created in collaboration with other networks.

Research Involving Outpatient Settings Network
RIOS Net

N01-HC-45211

Robert Williams, MD, MPH

University of New Mexico
Albuquerque, NM

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Robert L. Williams, MD, MPH
Professor of Family and Community Medicine
University of New Mexico

Dr. Williams is Professor of Family and Community Medicine at the University of New Mexico and Director of RIOS Net. He received his MD degree from Baylor College of Medicine and his MPH degree from Harvard. Dr. Williams has worked as a primary care clinician with diverse, underserved communities in various US and international settings for over 25 years. While working in the US Indian Health Services he was named its national Clinician of the Year. He has also been a Robert Wood Johnson Foundation Generalist Physician Faculty Scholar and a Fulbright Senior Scholar in South Africa, and he has received several teaching awards during his career. His principal research interests relate to primary care and public health of culturally diverse and underserved communities, and he is considered an international authority on the topic of community-oriented primary care. He has been PI on a number of federal and foundation research grants and contracts and lead or co-author on over 40 peer-reviewed publications. In addition to being Director of RIOS Net, he is also the Director of PRIME Net, the consortium of eight primary care practice-based research networks formed under the BAA contract.

PROGRAM DESCRIPTION

The Research Involving Outpatient Settings Network (RIOS Net) is an innovative clinical research network -- a practice-based research network composed of clinicians serving predominantly Hispanic and American Indian populations. Prior work in RIOS Net has demonstrated the network's capacity to: 1) conduct research in a range of clinical research topics using diverse research methods, 2) collaborate with other research networks, 3) successfully conduct research involving traditionally underrepresented communities, 4) incorporate minority views in setting priorities, and 5) conducts research in settings that lead to better translation of research into practice.
RIOS Net responds to the NIH Roadmap with this proposal, the overall goal of which is to meet the call for expanded capacity and collaboration of research networks. Four project specific goals are proposed:

GOAL 1. Increase the scope of network activities to include new scientific questions, disciplines, and/or tools and approaches;

GOAL 2. Increase participation, including appropriate training, within the network to include new sites, new patient populations and/or new investigators;

GOAL 3. Facilitate the communication and cooperation of RIOS Net with one or more additional networks

GOAL 4. Expand the RIOS Net information technology infrastructure and linkage capability

Robert Williams, MD, MPH

PROGRAM ACCOMPLISHMENTS

The RIOS Net/University of New Mexico project has met all of its program objectives, in many instances achieving milestones well beyond those in the original goals. Some of the key highlights are:

- Formation, development and expansion of PRIME Net consortium of practice-based research networks – The original three collaborating networks including RIOS Net developed a MOA and a shared mission statement together with process structures to support ongoing collaborative research. The consortium is organized to conduct "primary care research to improve the health and well-being of the multiethnic patients and communities our members serve"; its emphasis is on communities that are traditionally underrepresented in clinical research. As a response to initial successes, the consortium has expanded to now include 8 networks – RIOS Net; CaReNet (UColo); SERCN (Morehouse); SPUR-Net (Baylor); CRN (UCSF); SOAR-Net (Wright State); MetroNet (Wayne State); LA Net (USC).
- Conduct of two preliminary studies testing collaborative – As an initial test of the decision-making, communications, data-collection structures of the PRIME Net consortium, two studies were conducted across the consortium, examining clinician management of hepatitis C and of chronic, non-malignant pain. Papers summarizing the findings of these studies have been submitted or are under development.
- Conduct of 6-stage, multimethod study of diabetes risk, acanthosis nigricans, and clinician behavior – The PRIME Net consortium is completing a multistage, multimethod study of acanthosis nigricans and clinician preventive counseling behavior change as a result of participation in a network study. Analysis is beginning.
- Flexible IT infrastructure to support network consortium – The creation of a set of flexible information system tools to support communication and data collection across the collaborative. Tools have been developed that take into consideration varying levels of IS acceptance, development, and sophistication in practices across the consortium.
- Expanded RIOS Net membership – Through various activities under the contract (member benefits, enhanced communications, outreach in practices, etc.) clinician membership in RIOS Net has grown by some 35% to 270 members.
- Consolidated structure to link community members into process – RIOS Net community outreach staff have expanded activities in communities served by network members, providing updates of network activities, seeking community approval of planned studies, providing education on study related topics, and gathering community input into future study priorities and methods. This community liaison is a critical function for enhancing clinical research in the minority communities represented in the network in order to overcome distrust of research and researchers.
- Consolidated structures to close feedback loop to clinicians – RIOS Net clinician outreach workers have enhanced their activities with network members, presenting individual study data, providing CME, recruiting new members, making individual contact in practices, facilitating member benefits, etc.
- Expanded scope of research and built collaborations with UNM Prevention Research Center, UNM Cancer Research and Treatment Center, and the developing UNM CTSA

– Under the contract, RIOS Net has expanded the scope of its research topics and designs and has entered into collaborative research with key institutional partners.

- Development of educational modules on clinical research, CBPR, study specific topics – RIOS Net staff have developed web-based modules posted on the network web-site for training in the conduct of clinical research, for training on community-based participatory research, and for clinical topics related to studies being conducted in the network.
- Expanded communications processes, including electronic, in-person, paper-based – Under the contract, RIOS Net has expanded its tri-level (public, network, individual member) web site, created and regularly updated a web site for PRIME Net, expanded use and reach of listserve communications, increased one-on-one contacts with individual members, and increased the frequency of paper-based communications.
- Enhancement of member meetings with former US Surgeon General, Congressman, state senator in attendance – With support from the contract, the RIOS Net annual member meeting has grown in scope and attendance. At the most recent meeting, former US Surgeon General David Satcher, US Congressman Tom Udall and NM State Senator Didi Feldman were part of an attendance of over 300. These meetings provide key contact with network members and assist in communications and prioritization of network projects.
- Electronic support for remote and anonymous data collection – RIOS Net IT staff have developed mechanisms for collection and transmittal to central servers of remotely collected data from a wide-range of IT ready practices. This includes messaging systems that selectively contact subsets of clinicians/subjects while maintaining anonymity.

Inventory and Evaluation of Clinical Research Networks
IECRN

ADB #N01-HC-45209; HHSN268200425209C:
under PICS 263-01-D-0182, Task Order #169

Stephen Durako, PI

Westat
Rockville, Maryland

BRIEFING BOOK SUMMARY

May 8, 2008

PRINCIPAL INVESTIGATOR

Stephen Durako
Vice President and Director of Clinical Trials Study
Westat

Stephen Durako is a Vice President of Westat and Director of the Clinical Trials Study Area of Westat's Health Studies sector. He has served as principal investigator, project director, or project manager on many clinical trials; clinical studies of cancer, HIV infection, blood-transmitted diseases, and other diseases; and epidemiologic studies. His experience extends to all aspects of corporate management and study management and operations, including study design, the development of protocols and standard operating procedures, the design of data collection forms, subject location, data collection and processing, quality control, data analysis, subcontractor selection and negotiations, and budget and schedule monitoring.

PROGRAM DESCRIPTION

The Inventory and Evaluation of Clinical Research Networks (IECRN) Project is part of the NIH Roadmap for medical research which seeks to improve health and to speed translation of these discoveries into practice. In particular, the IECRN is related to *Reengineering the Clinical Research Enterprise*, a Roadmap component which seeks to enhance the efficiency and productivity of clinical research by promoting clinical research networks that can rapidly conduct high quality studies capable of addressing multiple research questions. The IECRN project began in September 2004 and is ongoing.

The primary objectives of the IECRN project are as follows:

- **Inventory**: To develop an inventory and database of clinical research networks. The Inventory is a searchable database of eligible, participating clinical research networks that contains demographic information about each network and links to the trials associated with each network via ClinicalTrials.gov. These network data are available as "network profiles" on a public website at https://www.clinicalresearchnetworks.org. The Inventory data collection is ongoing. Project staff continue to add clinical research networks to the inventory as they are identified.
- **Descriptive Survey and Best Practices Study**: To describe organizational and operational characteristics of a sample of networks in several key functional domains and to identify and examine network best practices that lead to achievement of specified outcomes. These studies were completed in the spring of 2006 and the results presented at the National Leadership Forum on May 31 and June 1, 2006. Full reports can be found on the project website.
- **National Leadership Forum**: To conduct a National Leadership Forum to discuss the study findings, highlight selected best practices and disseminate this

information to the research community. The National Leadership Forum was held on May 31 and June 1, 2006.

Current Status

The Inventory has been available on the IECRN website since October 2005. Westat is currently working with the National Center for Research Resources (NCRR) to more effectively position the website as a resource for the Clinical Research Network (CRN) community. The activities currently in process include enhancements to make the website more user-friendly and more appealing (re-branding of the website). An on-line website user satisfaction survey was recently submitted to OMB. The survey data will identify users, the type of information they are seeking, its intended use, and their overall satisfaction with the website.

Currently the focus of the website is on the utility of the Inventory data to a clinical researcher, rather than the IECRN project. The challenge is to promote the inventory as a valuable resource to them. First we have to ensure clinical researchers are aware the Inventory is available to them and how it can be beneficial to their clinical research work. Promotion of the Inventory includes contacting CRNs with active websites to request posting of the website link on their network webpage, and broadcasting new Inventory website information (updated profiles, new networks, enhanced website capabilities, etc.) to researchers who have requested to receive this information. The goal for these dissemination efforts is to increase clinical research awareness of the Inventory through facilitating relationships and partnership-building, which should indirectly accelerate medical discovery to improve health and speed translation of scientific discoveries into practice.

PROGRAM ACCOMPLISHMENTS

The IECRN project began in September 2004 and is ongoing.

The three major goals of the IECRN project are to:

- Develop a publicly available inventory and database of clinical research networks. The Inventory is a searchable database of eligible, participating clinical research networks that contains demographic information about each network and links to the trials associated with each network via ClinicalTrials.gov. These network data are available as “network profiles” on a public website at https://www.clinicalresearchnetworks.org. The Inventory data collection, referred to as the “Core Survey” is ongoing. Project staff continue to add clinical research networks to the inventory as they are identified.

- Prepare a detailed description of existing practices and assessment of best practices within clinical research networks. The goal was to describe organizational and operational characteristics of a sample of networks in several key functional domains and to identify and examine network best practices that lead to achievement of specified outcomes. These studies were completed in the spring of 2006 and the results presented at the National Leadership Forum on May 31 and June 1, 2006. Full reports can be found on the project website.

- Conduct a National Leadership Forum on the results of the inventory and descriptive studies.

The first goal resulted in the creation of an online searchable inventory of clinical research networks that can be accessed via the IECRN web site, which has been renamed the Networks for Clinical Research website. The inventory currently contains 274 networks (per the project definition of a Clinical Research Network). The inventory will include new eligible networks as they are identified. Networks can be considered for inclusion in the inventory by accessing the Contact Us page on the Networks for Clinical Research web site at https://www.clinicalresearchnetworks.org.

The second and third goals were accomplished via the completion of a Core Survey with data on 244 networks that responded as of March 2006 and Descriptive and Best Practices studies with a subset of those networks. The information from the surveys and studies was analyzed and presented at a National Leadership Forum on May 31 and June 1, 2006. The study reports, presentations, transcripts, and web casts can be accessed via the Resources page on the Networks for Clinical Research web site at https://www.clinicalresearchnetworks.org.

Introduction

This summary encompasses information about the Networks for Clinical Research web site https://www.clinicalresearchnetworks.org which includes the Inventory of clinical research networks (CRNs) and other IECRN project information and reports. The data incorporated in the report are from the 6 month period beginning September 1, 2007 and ending February 29, 2008.

Revisions to Web Site

The Inventory has been available on the website for approximately 2 ½ years (since October 2005). Westat is currently working with NCRR on dissemination activities to more effectively position the website (particularly the Inventory) as a resource for the CRN community. These activities include enhancements to make the website more user-friendly and more appealing, posting an on-line website user satisfaction survey (recently submitted to OMB), and developing a paper to describe the accomplishments and findings of the IECRN (in development). Currently the focus is on the usefulness of the Inventory data rather than on the IECRN project. The challenge is to learn more about the information needs of the clinical research community, as well as whether they are aware of the existence of the Inventory and, if so, whether it is useful to them. The survey data will provide information on what users are looking for on the website, how they intend to use the information they find, and how satisfied they are overall with the Inventory. The plan is to promote the Inventory by contacting CRNs to request posting of the website link on their network webpage, and by broadcasting new Inventory website information (updated profiles, new networks, enhanced website capabilities, etc.) to those who have signed up to receive this information. Our goal for these dissemination efforts is to expand the website Inventory and, by facilitating relationships and partnership-building, indirectly accelerate medical discovery to improve health and speed translation of scientific discoveries into practice.

Westat also partnered with AHRQ so that Practice-based Research Networks (PBRNs) registered with AHRQ could submit their data to IECRN without having to complete two

surveys. IECRN Core Survey questions were incorporated into the annual AHRQ Registry data collection and responses are shared with the IECRN project to update the Inventory.

Project Activities

The project's current activities include

- Core Survey distribution to newly identified potential CRNs
- Posting profiles of new CRNs on Networks for Clinical Research Inventory web site
- Maintenance of the Networks for Clinical Research web site
- Annual updates of the existing clinical research network profiles on the Networks for Clinical Research web site
- Promotion of the revised Networks for Clinical Research web site

Network Profile Activity

The identification of new clinical research networks is ongoing. Potential networks can go to the Contact Us feature on the web site or can be recommended by others in the clinical research field. All potential new networks are researched by program staff for eligibility. Networks found to be eligible per the project definition of a CRN receive the IECRN Core Survey. The survey data are then organized into network profiles. Each network reviews and approves the preliminary profile before it is publicly available. Starting in January 2008 the profile update reminders will be sent to all the networks during the first month of the year. As of the end of February 2008, 35 updates to the network profiles were received for this year.

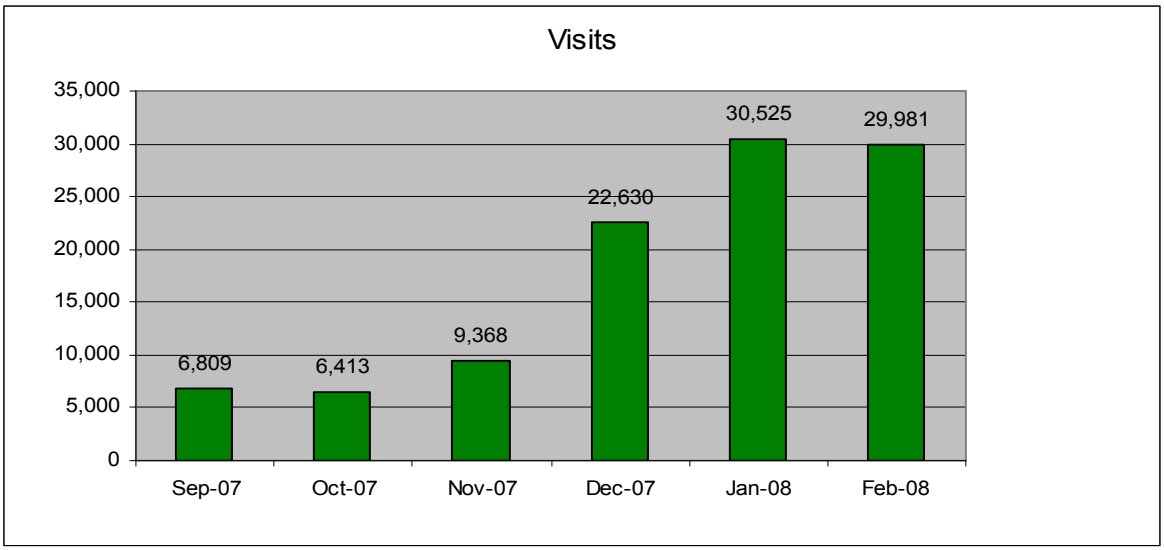
2.2 General Web Site Statistics

The General Statistics table below provides an overview of the activity the IECRN web site from September 1, 2007 and ending February 29, 2008. The data are compiled from WebTrends, a commercial off the shelf software package used by Westat to track web site activity.

Activity[4]	September 1, 2007 - February 29, 2008
Total Hits	296,526
Average Hits per Day	1,629
Total Visits	102,947
Average Visits per Day	565
Average Visit Length	8 minutes 48 seconds
Median Visit Length	11 seconds
Unique Visitors	40,752
One-time Visitors	31,071
Repeat Visitors	9,681
Most Active Day	February 27, 2008
Number of submitted profile updates[5]	35

[4] Activities are defined in a glossary at the end of the report.

The Visits graph below displays the overall number of visits by month to the IECRN web site from September 1, 2007 and ending February 29, 2008.



The Top Pages table below lists the most frequently visited pages on the IECRN web site from September 1, 2007 and ending February 29, 2008. Latest viewing statistics suggest web visitors are interested in the network profile pages. Profile updates with networks in the Inventory are conducted annually. The latest update requests were sent in January 2008. Web site visitors are also browsing the network listings and accessing multiple profiles during a browse session. The large volume of visits to the Join Inventory page appear to be spam emails. All emails received are reviewed daily to identify legitimate email requests

Top Pages

	Pages	Views	% of Total Views	Visits ▼	Avg. Time Viewed
1	/redirecthttps.htm (Redirect to Home Page)	98,153	39.31%	69,979	00:00:23
2	/default (Home)	96,306	38.57%	69,087	00:05:39
3	/profile.asp (Individual Network Profiles)	33,218	13.30%	13,796	00:05:19
4	/register.asp (Join Inventory)	3,512	1.40%	3,029	00:01:22
5	/forum.asp (National Leadership Forum)	2,080	0.83%	1,735	00:01:23
6	/summaries.asp (Listing of Networks via searches or browse)	2,257	0.90%	1,488	00:01:42

The Most Downloaded Files table lists the most frequent files downloaded from the IECRN web site from September 1, 2007 and ending February 29, 2008. Latest web site visitors mostly downloaded the Best Practices Profiles of Networks. The reports from the Core and Descriptive Survyes were also of interest to web site visitors.

Most Downloaded Files

	File	No. of Downloads	% of Total Downloads	Visits
1	\BPNetwork Profiles.pdf (Best Practices Profile of Networks)	1,057	5.31%	214
2	\Reports.pdf (Complete Project Report	997	5.01%	106
3	\CD2.pdf (Core and Descriptive Survey Report; Chapter 2: Core and Descriptive Survey Methodology)	737	3.70%	520
4	\BP2.pdf (Best Practices Study Report: Chapter 2: Best Practices Study Results)	581	2.92%	150
5	\CDReport.pdf (Core and Descriptive Survey Report)	540	2.71%	143

Glossary

Glossary	
Hits	A single action on the Web server as it appears in the log file. A visitor downloading a single file is logged as a single hit, while a visitor requesting a Web page including two images registers as three hits on the server; one hit is the request for the .html page, and two additional hits are requests for the downloaded image files. While the volume of hits is an indicator of Web server traffic, it is not an accurate reflection of how many pages are being looked at.
Average Hits per Day	Number of successful hits divided by the total number of days in the log.
Visits	All the activity of one visitor to a Web site. If a visitor is idle longer than the idle-time limit, it is assumed the visit ended. If the visitor continues to browse the web site after they reach the idle-time limit, a new visit is counted. The default idle-time limit is thirty minutes, but can be changed in Options.
Averaged Visits per Day	Number of visits divided by the total number of days in the log.
Average Visit Length	Average number of minutes the Web site was viewed by a visitor.
Median Visit Length	Median of non-zero length visits in the log. Half the visit lengths are longer than the median, and half are shorter. This number is often closer to the "typical" visit length than the average visit length. Numbers that are wildly atypical can skew the average, but will not skew the median so much.
Unique Visitors	Individuals who visited the web site during the report period. If someone visits more than once, they are counted only the first time they visit.
One-Time Visitors	Individuals who visited thew web site only once during the report period.
Repeat Visitors	Individuals who visited the web site more than once during the report period.

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MCRC – Lee Green, MD

RESEARCH IN ROUTINE CLINICAL WORKFLOW: THE MICHIGAN CLINICAL RESEARCH COLLABORATORY EXPERIENCE

INTRODUCTION: The Michigan Clinical Research Collaboratory (MCRC) project had three primary goals: 1) Build and test a Clinical Research Information Fabric (CRIF) to provide secure, HIPAA-compliant data exchange between a clinical trials support system, a cardiology interventions registry database, a depression case management system, and a primary care clinical quality management system; 2) achieve semantic interoperability of the data elements in the CRIF; and 3) conduct a feasibility study to demonstrate the effectiveness of this collaborative system in practice. This poster reports the results of the feasibility study.

METHODS: We conducted a prospective observational cohort study of depression symptoms among patients with coronary heart disease. The implementations were structured to merge the study activity (consent forms, data collection, and follow-up) into regular clinic workflow, linking the CRIF to existing IT infrastructure in the practices while the CRIF's centerpiece, the Honest Broker, worked behind the scenes, gathering data from the other systems and passing data to them as clinically appropriate. The study sites were four primary care practices in a practice-based research network: one urban private practice, one urban free clinic for the underserved, one suburban private practice, and one rural underserved practice.

RESULTS: Over 60% of all patients at the practices who were eligible were entered into the study; over 70% of eligible were entered at the largest site. Unique solutions were required at each practice, even those that were members of the same large group. The IT effort in creating the CRIF was straightforward. The IT integration in practices required much more effort than anticipated, required several iterations, and was heavily determined by practice rather than project staff.

CONCLUSIONS: By integrating research into clinic workflow, PBRN practices can enroll patient samples promising excellent external validity. Resources must be refocused from academic medical centers to practices to accomplish this. IT integration was expected to be a technology challenge but depended more on close collaboration between IT and clinic staff.

A CLINICAL RESEARCH INFORMATION FABRIC: THE MICHIGAN CLINICAL RESEARCH COLLABORATORY INFRASTRUCTURE

The Michigan Clinical Research Collaboratory (MCRC) project had three primary goals: 1) Build and test an Honest Broker to provide secure, HIPAA-compliant data exchange between a clinical trials support system, a cardiology interventions registry database, a depression case management system, and a primary care clinical quality management system; 2) achieve semantic interoperability of the data elements between these systems; and 3) conduct a feasibility study to demonstrate the effectiveness of this collaborative system in practice. This poster reports the final infrastructure development: the creation of the Clinical Research Information Fabric (CRIF).

The CRIF is a federated approach to integrating heterogeneous clinical datasets for research purposes. The CRIF duplicates data where necessary; e.g., data from a subject's

clinical history are duplicated into the clinical research data set. The centerpiece is the Honest Broker (HB), which assigns a random number to research subjects, so other unique identifiers considered HIPAA-Protected Health Information (PHI) are never used. PHI is not duplicated into research data sets, so a loosely-coupled connection between clinical and research databases is used to transfer data between these repositories. The process is coordinated by the MCRC Informatics Core. The other major portions of the CRIF are operational patient care systems: the Michigan Depression Outreach and Collaborative Care (M-DOCC), Michigan Cardiovascular Outcomes Research and Reporting Program (M-CORRP), and ClinfoTracker, a primary care patient registry and clinical reminder system. The CRIF seamlessly integrates them with the research system, Velos eResearch, to allow interdisciplinary research on co-morbid conditions.

The CRIF moves data among clinical users for patient care and quality improvement, while passing only consented information to the research system. It maintains security using dually-authenticated SSL communication. It operates as a SaaS model, using SOAP messages to pass data as well as actions called for by research protocols. The feasibility study (reported elsewhere) has demonstrated it in practical operation.

AGNIS – Dennis Confer, MD

THE THREE FACES OF AGNIS.

Dennis L. Confer (PI)[1], Mary M. Horowitz[2], Douglas Rizzo[2], Ken Bengtsson[1] and Martin Maiers[1]

[1]National Marrow Donor Program (NMDP), Minneapolis MN. [2]Center for International Blood and Marrow Transplant Research (CIBMTR), Milwaukee WI.

AGNIS is the acronym for A Growable Network Information System. It is a public system that facilitates controlled, automatic and secure sharing of authorized data between multiple, dissimilar database systems. AGNIS eliminates multiplicative data entry activities because data will enter the electronic network once with AGNIS facilitating subsequent distribution and synchronization between databases. AGNIS also eliminates data drift, which occurs when the same data are replicated in multiple databases in the absence of consistent update and audit controls. AGNIS is distributed under a public license at www.agnis.net. The sponsors of AGNIS are the NMDP and CIBMTR, which are organizations collaboratively facilitating multi-center research in hematopoietic stem cell (HSC) transplantation. More than 450 HSC transplant programs, many with their own electronic databases, submit data to the databases of NMDP or CIBMTR and these programs comprise the user base of AGNIS. We have envisioned three implementations of AGNIS.

THE FIRST FACE: INTEGRATED AGNIS. This implementation places AGNIS between two high-end database systems exemplified by a major high-volume HSC transplant program connected to a central NMDP/CIBMTR database. The transplant program database may incorporate connections to EMRs and/or laboratory data systems. An AGNIS node sits at each end. The AGNIS data elements, which are specified in the NCI's caDSR (National Cancer Institute's cancer Data Standards Repository), must be specifically mapped into each high-end database. The mapping task is reduced or eliminated by adopting some or all of the AGNIS data elements in the high-end databases.

THE SECOND FACE: 3RD PARTY AGNIS. In this model, the HSC transplant program has purchased a 3rd party database system that incorporates AGNIS communications. Data mapping at the local transplant center is not necessary because this step is incorporated into the 3rd party offering. Connectivity to EMRs or laboratory database systems is limited, but the transplant program benefits from a local database system with built-in reporting and analysis features, as well as the capability for adding relevant local data, e.g., referring physician contacts. This model is being pursued by several software firms.

THE THIRD FACE: AGNIS ALONE. In this model, the AGNIS node at the HSC transplant program serves as the program's local database, primarily receiving data that have been entered centrally. This model is the least expensive and probably least flexible for the local program. It requires AGNIS enhancements that remain under development, including a reporting database and tools for administration, editing and limited queries.

We conclude that AGNIS provides flexibility and implementation options adaptable to multiple users whose needs and resources are highly varied.

TB TRIALS – Carol Dukes-Hamilton, MD

HUMAN SUBJECTS PROTECTION AND ALTERNATIVE IRB USE: AN ASSESSMENT OF THE EXPERIENCES AND ATTITUDES OF LOCAL INSTITUTIONAL REVIEW BOARDS ON THE USE OF CENTRAL OR COOPERATIVE REVIEW MECHANISMS FOR MULTICENTER STUDIES

Carol Dukes Hamilton, MD
Duke University Medical Center

BACKGROUND: Two comprehensive reviews of the human subjects protection system (IOM, National Bioethics Advisory Commission) recommended evaluation of alternatives to the current system of local IRB review of multicenter studies. Current regulations allow one IRB to cede oversight of a protocol to another IRB. However, there has been limited acceptance of central or cooperative review of multicenter studies by local IRBs.

RESEARCH OBJECTIVE: Assess local IRBs' attitudes and experiences with central or cooperative review and identify barriers to more widespread use.

METHODS: We initiated a "call for commentary" from the Chairs of 139 US-based single-institution IRBs that served one or more of the following: the Tuberculosis (TB) Trials Consortium, the TB Epidemiological Studies Consortium, Schools of Public Health, State Health Departments, and the top 125 NIH-funded institutions. The final instrument consisted of seven questions or statements regarding central IRB or other cooperative review arrangements, as well as space for open-ended comments. Responses were not linked to individual IRBs. The analysis used simple descriptive statistics summarizing responses to individual questions

RESULTS: We had an overall response rate of 45% (63/139). Of the 63 responding institutions, 43 (68%) reported ceding oversight to another IRB within the past 3 years. Eight (13%) had not ceded oversight but were willing to consider it. The remaining IRBs were either unwilling to consider a cooperative review mechanism (8 [13%]) or had no specific policy on the issue (4 [6%]). Of the IRBs that had used a central or cooperative review mechanism, 23 (50%) were satisfied with the arrangement, 3 (7%) were not satisfied, 19 (41%) were neutral, and 1 (2%) did not answer. The central IRB of the National Cancer

Institute (NCI) was the most common central review group reportedly used. Regarding future plans for use of cooperative review of multicenter protocols, 61% planned to use central/cooperative review, while 28% were cautious/unsure about future arrangements. Regarding the adequacy of human safeguards with central/cooperative review, 50% thought that using a central IRB provided fewer safeguards; 46% reported no difference in safeguards with central vs. local review.

CONCLUSIONS: A majority of the IRBs responding had used central or cooperative review of multicenter studies, most often the central IRB of the NCI. Most were satisfied with their experience and planned to continue to use central/cooperative review. However, it is concerning that 50% thought that central/cooperative review provided fewer safeguards to human subjects.

NEXT STEPS: In collaboration with the Roadmap Human Subject Protection Working Group (HSP WG) a manuscript will describe the products of the aim and we will offer a framework for considering alternative IRB review mechanisms, including key issues such as roles and responsibilities under different models, and an exploration of potential applications, strengths and concerns.

IDENTIFY AND REDUCE BARRIERS TO CONDUCTING CLINICAL RESEARCH: ENHANCING THE U.S. PUBLIC HEALTH SYSTEM'S WILLINGNESS AND CAPACITY TO ENGAGE IN CLINICAL RESEARCH

Carol Dukes Hamilton, MD
Duke University Medical Center

PROJECT GOALS:

- Work with principal investigators and study coordinators of the CDC- funded, Tuberculosis Trials Consortium (TBTC) to identify and reduce barriers to conducting clinical research in public health clinics. A 8000 patient, international, TBTC clinical trial (Study 26) was the base of the project.
    - Determine metrics for evaluation
    - Identify and recruit sites
    - Conduct site visits
    - Analyze data and issue recommendations for the intervention
    - Evaluate the efficacy of the intervention(s)
    - Report findings

STUDY DESIGN & METHODS:

- Duke collaborated with Research Triangle Institute (RTI) to develop methodology and approach
- Duke and RTI teams met with TBTC members to form "Barriers to Research" Team
- Refined study goal and objectives and define metrics.
- Identified 12 sites based on the following criteria to ensure diversity:
    - Geographic region
    - Study 26 enrollment rate
    - Setting (academic vs. public health)
- RTI conducted site visits to observe program operations and meet with TBTC and public health staff to explore:
    - Study 26's, history and context, structure, and processes

  - Relationships and communication between study coordinator and site staff
  - Research attitudes and training among site staff
- Duke and RTI developed intervention focusing on:
  - Improving communication
  - Increasing Study 26 training opportunities
  - Utilizing Study 26 resources (quick reference guide, promotional materials)
- Disseminated intervention materials to study coordinators. Initial rollout of the intervention occurred in November 2006 and a booster was provided in July 2007. Materials included:
  - 'Quick Reference Guides'
  - Study 26 'Talking Points'
  - Study 26 brochures and promotional materials
- From December 2006-November 2007, conducted monthly telephone assessments with study coordinators and a designated clinic staff person from each site to capture:
  - Frequency of communication, Study 26 training, and advertisements for training
  - Distribution and use of Quick Reference Guide
  - Distribution and receipt of study status reports

ANALYSIS:

- Developed an analysis plan to measure adherence (process evaluation) to and impact of the intervention (outcome evaluation).
- Process Evaluation Questions: (1) How did adherence vary between sites with different recruitment success? (2) How did adherence differ between Intervention Phases I (November 2006 to June 2007) and II (July 2007 to November 2007)?
  - Analyzing monthly assessment data to quantify adherence measures and to identify emergent themes within and across sites that may have affected study enrollment (e.g., staff turnover, local TB outbreaks).
- Outcome Evaluation Questions: (1) How did enrollment vary between sites with different recruitment success? (2) How did enrollment differ between Intervention Phases I and II?
  - Analyzing Study 26 enrollment data provided by CDC

RESULTS:

- Study findings will be presented at the May 2008 TBTC meeting in Toronto, Canada.

CREATING THE METHODOLOGY TO CREATE THERAPEUTIC AREA DATA STANDARDS

Carol Dukes Hamilton, MD

Duke University Medical Center

This purpose of the Data Standards Aim was to design a methodology for developing therapeutic area data standards for tuberculosis (TB) to be used in healthcare, at the point of data collection, that supports multiple reuses in surveillance, research and decision support. The project's goal also includes creating real products that can be applied to specific use cases.

The design of this project included following the ANSI standards development process that promotes the engagement of key expert stakeholders to develop the standards. What was

also important was develop a relationship with standards organizations (SDOs) that are experts in the field of developing healthcare and research standards. We also started this process by gathering data elements currently in use by the TB community. Because of the amount of data elements received the stakeholders decided to start with a subset of data elements focusing on the treatment and diagnosis of Pulmonary TB called Package #1. Documenting the process and lessons learned was a key activity during this process.

As a result of this project a number of artifacts have been produced that we believe describe and documents the clinical domain of Tuberculosis. There are 91 data elements and over 300 possible response items called permissible values that have been produced. The process for developing a process for representing TB activities and data associated with them is valuable but it was clear that the industry view of developing standards is limited to creation and not maintenance and governance.

Although there has been significant work in creating data standards accomplished there are still other data elements to standardize and implementation designs to complete this therapeutic domain. More importantly, there are critical questions remaining surrounding issues of maintenance, stewardship and long term use that need to be reconciled for the project to be successful.

DECISION MODELS FOR TB PREVENTION AND TREATMENT: DEVELOPMENT AND DISSEMINATION OF EVIDENCE-BASED DECISION MODELS FOR TB PREVENTION AND TREATMENT

Carol Dukes Hamilton, MD
Duke University Medical Center

Currently there are several available methods for reducing the effect of TB in the population as well as ongoing research into novel treatment and prevention techniques. How best to use our limited health and economic resources towards achieving the overall goal of TB eradication however is uncertain. Our objective was therefore to develop a Markov decision model to estimate the short- and long-term economic costs and health benefits of current and proposed programs for the reduction of tuberculosis in the U.S. population. We also sought to incorporate this model into an automated web-based system (ALCHEMIST) which allows policy makers to explore the underlying model and findings, and to tailor the evidence to reflect the population of interest.

We developed a Markov model to evaluate the different available mechanisms for reducing TB's burden of disease including: vaccination, prevention programs, and treatment of infected individuals. We model the underlying prevalence of TB in the population and the natural history of the disease as well as the various components of the prevention and treatment strategies. For each strategy we evaluate lifetime costs, life expectancy, quality-adjusted life expectancy, and incremental cost-effectiveness. Sensitivity analyses account for important model uncertainties and assumptions.

Once developed, a mechanism is needed to disseminate the evidence-based decision model and to tailor it to specific patients and populations. In prior work, we developed ALCHEMIST, a web-based system that generates evidence-based management recommendations automatically from decision models. ALCHEMIST is independent of any particular clinical domain and may be used with any structured decision model. ALCHEMIST analyzes a decision model, automatically extracts information from the model

representation, and creates a decision model annotation editor that solicits additional knowledge from the decision analyst. ALCHEMIST then uses this information to create a "global" management recommendation for a typical patient. In addition to a flowchart algorithm that shows the optimal recommended strategy, ALCHEMIST displays the guideline objective (including the targeted health problem and patient population), the available options or alternatives, the health and economic outcomes identified, the underlying evidence used to generate the recommendations (including the methods for obtaining this evidence, the quality level of the evidence, and what ranges of values were used in sensitivity analyses), the methods used to obtain and order patient preferences, a balance sheet of the benefits, harms, and costs for the alternative strategies, a graphical representation of the change in the expected utility of a given strategy as each variable value is varied along its sensitivity-analysis range, a list of the variables to which the recommendation is sensitive, and sponsors. This set of documents is then made available over the web; any user can customize it to specific clinical settings, and guideline developers can modify it over time as the underlying decision model or evidence evolves. ALCHEMIST is designed to improve the applicability, relevance, and acceptance by local users of management recommendations.

In this poster we will describe the structure of the decision model, the data needed for its analysis and the current uncertainties in the available literature. We will demonstrate how the model allows us to explore the following clinical and policy questions: (1) What are the economic costs and benefits of available TB treatment and prevention programs? (2) What is the most cost-effective allocation of limited healthcare resources to reduce the TB burden of disease? (3) How do the available programs differ in terms of the number of TB cases prevented? and (4) What variables are the results most sensitive to – and how do these analyses help prioritize future data acquisition? We will then provide a demonstration of the ALCHEMIST system to the under-development TB model. This interface will allow users to examine a list of model assumptions, and review base-case values and ranges for model variables. ALCHEMIST initially generates global recommendations that apply to an "average" patient population, but the local guideline user is able to make the recommendations applicable to a specific site or patient by either tailoring the input variables or by limiting or expanding the range of strategies available.

We believe the integration of the TB decision model with the ALCHEMIST system will help facilitate evidence-based management of a complicated problem in healthcare resource allocation and may improve the ability of decision makers to incorporate systematic analyses into both policy and clinical decisions.

CTNBP – Robert A. Harrington, MD, FACC

DEVELOPING THERAPEUTIC DATA STANDARDS IN CARDIOLOGY

Robert A. Harrington, MD, FACC; Brian McCourt, BA, CCDM; Kathleen Fox, RN, BS; Meredith Nahm, MS, CCDM

OBJECTIVE: The ability to exchange healthcare data across multiple sites and for multiple purposes, including research, has become a national priority due to demands for:

- Patient safety
- Creation of electronic health records with reusable information
- Health surveillance
- Performance measures
- Quality improvement
- Biodefense
- Continued examination of important clinical research questions
- And more

All of these issues point to an unparalleled need to maximize the use of data captured within the clinical environment. As healthcare documentation is primarily unstructured text, its reuse in meeting these demands is extremely limited. In conjunction with a national and international movement to develop common clinical and technical data standards, the Duke Clinical Research Institute and a network of stakeholders are working to develop a model methodology for the creation and implementation of therapeutic area standards, with acute ischemic heart disease as the initial focus. This work is being done in collaboration with a tuberculosis initiative lead by Dr. Carol Dukes-Hamilton; both initiatives are being conducted under the NIH Roadmap program.

METHODS: With a focus on facilitating open discussion and promoting resources, the methodology will:

- Engage stakeholders representing healthcare, pharmaceutical and device industry, professional societies, government agencies, payers, and standards development organizations in addressing functional interoperability and semantic interoperability from a therapeutic domain perspective
- Produce, by consensus, a set of data elements, including clinical definitions, mappings to controlled vocabulary, and valid value lists, which will provide a foundation for data standards
- Identify, support, and develop HL7 standards that will facilitate data interchange within and across healthcare organizations
- Develop a CDISC implementation using cardiovascular data to enable standardized submission of data to the FDA and within the biopharmaceutical industry
- Implement the standards in a pilot project using real, valuable scenarios and live clinical data
- Create a sustaining infrastructure to support continued development of cardiovascular data standards that address contributions to standards development organizations, maintenance of the master set of data elements, coordination and engagement of the many stakeholders and development of future leaders in cardiovascular informatics

- Report detailed lessons from this tested methodology and recommend to stakeholder leadership the infrastructure, resources, and tools needed to support development of therapeutic area data standards

RESULTS:

- Key stakeholders representing over 30 organizations have been enlisted to participate in the development of common data standards for ischemic heart disease.
- Ten sets of data elements are in progress of aggregation using an ISO 11179-based model, aligned with future incorporation in the National Cancer Institute Enterprise Vocabulary Service caDSR repository.
- A new HL7 Cardiology Special Interest group has been formed in support of therapeutic area standards development.
- CDISC has initiated work, with initial focus on Study Data Tabulation Model, to support the standardized interchange of cardiovascular data.
- A draft pilot project plan has been outlined, and discussions with participating organizations have begun.
- An outline of a sustained, supporting infrastructure has been created.

CONCLUSIONS: The results to date have been significant and are expected to yield substantial benefits for the entire healthcare community. Our approach of demonstrating the methodology through the creation of the infrastructure has the dual advantage of both enabling tangible, long-term results while, at the same time, vetting the methods and objectives in a wide forum of stakeholders. Additionally, momentum has developed that will sustain the activities beyond the life of this project. The broader goal of supporting functional and semantic interoperability appears attainable and progress can be hastened by a coordinated effort to develop cross-cutting therapeutic area data standards.

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CONFLICTS OF INTEREST: None

OFFERING CLINICAL-RESEARCH TRAINING, TOOLS, AND TEMPLATES VIA A WEB SITE PROVES SUCCESSFUL

Robert A. Harrington, MD, FACC; Renee L. Pridgen, BA, CCDM; George M. West, Jr., BA

OBJECTIVE: To provide an online community that serves as a central repository of training, tools, and templates for clinical research coordinators to enhance site abilities to perform clinical research.

METHOD: After identifying the need for a central repository of training, tools, and templates for clinical research coordinators, the Clinical Trials Networks Best Practices (CTNBP) project launched a public Web site in January 2006. As of June 2007, with an average of

approximately 10,000 visits per month, the Web site, https://www.ctnbestpractices.org/, not only has affirmed this need, but has proven to be an ideal information platform.

In October 2004, the NIH began funding the CTNBP project under its Roadmap initiative Reengineering the Clinical Research Enterprise. CTNBP created a Study Coordinator Advisory Committee (SCAC) to address one of the project's 4 aims: making programs and tools available to improve site recruitment, retention, and performance.

The SCAC consists of 10 research coordinators representing 9 clinical sites. The SCAC identified a major challenge to clinical sites: sites spend too much time and money seeking resources—such as training and templates—essential to conducting research. Located in various places, these resources often are not advertised well. For clinical sites new to research, especially, finding and funding adequate resources is often prohibitive.

The SCAC identified the need for a central, low-cost means of offering programs and tools for research coordinators. To accomplish this, they proposed a Web site and began identifying tools and templates to post. The SCAC also recognized that a Web site would mesh well with the other project aims to apply information technology across multiple networks, to provide a repository of tools and programs to help sites conduct research, and to encourage communication across sites and networks.

Input on content comes from other CTNBP teams, in addition to the SCAC: academic/professional specialists in project and site management, statistics, data collection, informatics, and communications; research networks representing multiple therapeutic areas; and site investigators. Content is evaluated and improved using Web site workgroup areas and, after approval, is posted in the public area of the Web site.

RESULTS: In January 2006, CTNBP opened the Web site to the public. Visits to the site have increased from 246 in January 2006 to 10,530 in May 2007. The Web site received over 10,000 visits each month during March through May 2007.

The Web site's most popular content is online training for clinical site personnel who do not have the time or budget to travel for training. Training topics include a clinical research overview, building a successful research site, Good Clinical Practice, and human research subject protection. Trainees complete programs at their own paces, and many courses offer CMEs for $15 or free CEUs.

The SCAC continues to identify, review, and tweak Web site content. CTNBP promotes the Web site via annual conferences for multiple therapeutic areas, investigator and coordinator meetings, and word-of-mouth. CTNBP receives feedback on Web site content via online tools, lessons-learned sessions, and communication with visitors/project teams, and then incorporates input into currently posted content as appropriate.

ACKNOWLEDGEMENTS: We greatly appreciate the participation, guidance, and support received from the following individuals who make up the Study Coordinator Advisory Committee: Kimberly Broadway, RN, BSN; Terri Campbell, RN, CCRC; Roger DeRaad, RN, CNS, CNP; Bernadette Druken, RN; Karen Dwyer, RN, BSN, CRCC; Kathleen Kioussopoulos, RN, BSN; Kelly Maresh, RN, BSN, CCRC; Catherine Neva, RN, BSN, CCRC; Deborah Zimmerman, RN, BSN, CCRC; Helen Zimmerman, MSN, CRNP .

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CONFLICTS OF INTEREST: None

INTERTRIALS – Stephen Johnson, PhD

THE InterTrial PROJECT IN THE COLUMBIA UNIVERSITY-NEW YORK PRESBYTERIAN HOSPITAL CLINICAL TRIALS NETWORK

The NIH Roadmap initiative is exploring methods to reengineer the clinical research enterprise. Clinical research networks provide an intriguing paradigm for this effort, by forging new partnerships among academic researchers, community-based physicians, and community patient organizations. The Clinical Trials Network of Columbia University and New York Presbyterian Hospital has explored one particular model, in which a research support hub located at an academic medical center coordinates trials in a network of community-based practices located in the New York City area.

Experience before the Roadmap project suggested that information technology improve administrative activities required to manage the network, thus improving the efficiency of network operations. However, little is known about how information technologies (IT) and informatics solutions are employed in community settings. Both academia and business, have encountered significant challenges when implementing IT solutions. Not the least is the need to change the behavior of individuals and groups in complex organizations in order to capitalize on new technologies.

The InterTrial project tried to understand these challenges using the IT Implementation Framework, which requires diagnostic analysis before implementing new IT. This model analyzes the facilitators and barriers to behavior change and uses the results to inform a change in management approach. InterTrial, our Roadmap project, conducted a series of qualitative and quantitative studies of clinical research in community practice settings. In one project, we studied the deployment of STEPS (Services Tracking and Expedited Payment System), software that supports community research sites by facilitating reimbursement. Also, we studied the workflow needs of clinical research coordinators used our findings to develop our WorkWeb software, which permits sharing of calendars, documents and other workflow support tools. Our findings suggest that there are significant barriers that impede efficient clinical research: lack of well-designed tools to support clinical research workflow, lack of models to represent clinical research processes, and inadequate support for research infrastructure. New kinds of software tools can address some of these issues, but re-engineering clinical research also requires changes in research administration and business practices.

THE COLUMBIA UNIVERSITY CLINICAL TRIALS NETWORK

Bigger JT, Busacca LV, Ennever JF, Steinman RC, Florenz M

BACKGROUND: Since 2003, NIH has expended substantial energy on re-engineering the clinical research enterprise as part of its Roadmap initiative. The NIH Roadmap proposal includes a large national network of community medical practices that have trained personnel prepared to quickly start NIH-sponsored clinical trials to capitalize on new basic science and early translational findings that raise the hope of diagnostic or therapeutic advances. To pursue this vision, NIH has funded a variety of exploratory projects: surveys of existing clinical trials networks, small-scale network development ventures, and development of information technology infrastructure. Also, the NIH contracted RAND Corporation to advise it on how to structure a large national community-based clinical trials

network. The RAND report was based on surveys of clinical trials networks and organizational theory. In parallel with, but independent of, these efforts by NIH, we established an experimental community-based network to conduct randomized clinical trials.

METHODS: The Clinical Trials Network comprised five therapeutic groups ─ General Medicine, Cardiology, Gastroenterology, Neurology, and Oncology ─ supported by two units at Columbia University: an administrative unit (contracts, budgets, etc.) and a Research Support Hub (RSH), featuring a telephone hot line and regular site visits, to assist with regulatory and IRB affairs. Coincidentally, many of our procedures tested RAND theories.

RESULTS: During a 5-year pilot study, we conducted 37 randomized clinical trials using subsets of 39 community clinical research sites. Sites screened and enrolled trial participants efficiently and retained them well. We encountered several operational problems at sites, e.g., research personnel with variable workflow skills, slow start-up, incomplete documentation of research services by sites, slow payment, and fluctuating research activity. We found solutions for most, but not all, of them. We developed software, called STEPS+, to guide research coordinator workflow, i.e., the conduct and documentation of research visits and procedures. This software also facilitated documentation of research services, making reimbursement faster and more accurate. The RSH liaison position was critically important for early detection and resolution of problems at the sites.

CONCLUSIONS: We found strong central support, regular quality assurance visits, facilitation of networking between clinical sites and organizing clinical research by therapeutic groups useful for improving the research enterprise. We think that our experience will encourage and assist the NIH in its effort to develop a national clinical trials network.

COLUMBIA UNIVERSITY – DEMONSTRATIONS

Demo 1: STEPS+ (Service Tracking Evaluation and Payment System)

We will demonstrate STEPS+, a clinical trials data management system that helps manage participant visits, fee-for-service reimbursement, and CRC workflow. We will demonstrate how to enter visits, how to enter non-protocol-related events, and how to view upcoming events on a "to-do" list and calendar.

Demo 2: WorkWeb

We will demonstrate WorkWeb, a common software infrastructure for hosting social network applications. We will show two such applications, WorkWeb/Columbia and WorkWeb/STEPS. WorkWeb/Columbia is a social network of Columbia investigators that provides profiles of investigators and their associations and collaborations, such as departments, centers, grants, and publications. WorkWeb/Columbia is the first social network application hosted by WorkWeb.

The initial prototype of WorkWeb/STEPS provides a social network view of a clinical research site, with profiles for the site itself, staff, studies, participants, and visits. WorkWeb/STEPS will also incorporate customized functionality required by a clinical research site".

CNIC – James Kahn, MD

DEVELOPING SYSTEMS TO INTEGRATE HIV GENOMIC DATA INTO THE CFAR NETWORK OF INTEGRATED CLINICAL SCIENCE (CNICS) CLINICAL DATABASE.

J Kahn[1], C Mathews[2], M Saag[3], M Kitahata[4], B Rodriguez[5], SDW Frost[6], S Boswell[7], WB Lober[4], M Lederman[5], S Sun[2], T Nunnery[1], M Roberts[1], R Moore[8] and RH Haubrich[2], for the CNICS Study Team

[1]University of California San Francisco, San Francisco, [2]University of California, San Diego; San Diego, California; [3]University of Alabama, Birmingham; [4]University of Washington, Seattle; [5]Case Western Reserve University, Cleveland; [7]Fenway Community Health/Harvard Medical School , Boston.; [8]Johns Hopkins Hospital, Baltimore, MD

BACKGROUND: To develop and implement a system that integrates HIV-1 resistance test information (FASTA genotype nucleotide sequences and phenotype assays) into a research repository. The focus of this project is to extend and apply new technologies to an existing research network by developing standards for the automatic download of viral resistance data into electronic health records (EMRs), to populate the research network's central data repository and utilize analytic strategies and statistical methodology to define the effect of cumulative HIV resistance on the pace of development on disease progression.

METHODS: The lab generates a genotype sequence file and/or phenotype resistance file for each sample, which are returned to the requesting site. After a local QA process the files are uploaded to the CNICS resistance database via a webpage. During upload the website validates each genotype sequence and phenotype data for header consistency. For every sequence in the FASTA file, headers are parsed and checked and header values are compared against lookup tables in the database for validity. After passing this initial validation, the nucleotide residues are counted. The header uses standard FASTA delimiters; i.e. header format is initialized with ">" and delimited by "|" (pipe). Phenotype data consists of IC50 (Inhibitory concentration 50%) of a wild type virus, the IC50 of the patient virus and the fold change, calculated by dividing the patient value by the wild type value. This data is provided for each drug that can be assayed, currently 17 drugs or drug combinations are assayed. Phenotype data requires text formatted files with the extension '.phc'. The extension is given to the files after being processed by the DTS package, ensuring the first level of format compatibility checking has been completed. The upload utility checks for the appropriate header elements and parses out the IC50 values. Genotype sequences are also checked for QA, a count of codons is performed, and the results o f a successful upload are written to the database and displayed on the website. Any errors that occur during upload or QA are logged by the database and an error page is generated. Phenotypic data from commercial labs. Tools used in this project include: Development Environments (Visual Studio); Programming Languages (ASP, Python 2.4; Visual Basic [Active X], JavaScript); XML tools (XMLMind XML Editor 2.10; Oxygen XML Editor 7.0) BioInformatics Tools and Libraries (BioPython 2.4, HyPhy 0.99, BLAST 2.2.9 and others) HL7, SQL Server 2000 and MIRTH.

RESULTS: Thus far we have uploaded more than 4,000 sequences and each CNICS site will upload data into the common repository. The repository at UCSD has been uploaded into the CNICS clinical database at UW. Analysis of regimens based on resistance has begun.

CONCLUSIONS: The group was able to identify and parse FASTA files, upload them into a common database and transfer the database to the clinical repository. Next steps will be to reuse the technology and apply it to the developing human sequences that are being performed for patients with HIV disease.

REPRESENTING COMPLEX REGIMEN DATA IN THE CNICS (CFAR NETWORK OF INTEGRATED CLINICAL SYSTEMS) COHORT

SDW Frost[1], C Mathews[1], M Saag[2], M Kitahata[3], B Rodriguez[4], J Kahn[5], S Boswell[6], WB Lober[3], M Lederman[4], S Sun[1], AFY Poon[1], S Jain[1], RH Haubrich[1], and the CNICS Study Team

[1]University of California, San Diego; San Diego, California, USA; [2]University of Alabama, Birmingham, United States; [3]University of Washington, Seattle, United States; [4]Case Western Reserve University, Cleveland, United States; [5]University of California San Francisco, San Francisco, United States; [6]Fenway Community Health/Harvard Medical School , Boston, United States.

BACKGROUND: In order to predict clinical response to therapy using observational databases, resistance data and regimen type need to be considered. While there are many algorithms to process and represent resistance data, little attention has been paid on how to represent and visualize regimen data in order to identify broad trends of regimen use over time.

METHODS: Regimen data were retrieved from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS), consisting of data from patients at six CFARs (Case Western, Fenway, UAB, UCSD, UCSF, and UW). Analysis was restricted to the first regimen for each individual obtained during the period 1996-2006 inclusive. Each unique regimen was represented as a hierarchy, in which drugs were annotated by gene targeted (envelope, protease, reverse transcriptase) and mode of action (NRTI vs. NNRTI, fusion inhibitor versus CCR5 antagonist). Similarity between different regimens was calculated using a subset tree (SST) kernel, normalized by tree size. The resulting kernel matrix of similarities was plotted using kernel principal components analysis, with statistical tests for differences by year and by site performed using a Maximum Mean Discrepancy (MMD) statistic.

RESULTS: A total of 307 unique regimens were observed in a database of 3721 individuals, comprising of combinations of 23 drugs. No clustering of regimens was detected when similarity was measured simply in terms of the number of drugs in common. By representing regimens as a tree, in which each drug is classified by gene and mode of action, we identified six major clusters of regimens. The frequency of these clusters varied by site, and over time, with dramatic annual changes in regimen until 2005, after which the composition of regimens remained relatively constant.

CONCLUSIONS: The large number of possible combinations of antiviral agents makes treating each regimen individually infeasible, yet lumping regimens into a small number of classes defined *a priori* may risk losing information. Our approach of representing regimens as trees avoids information loss, can help to identify clusters of regimens and temporal trends in extremely large observational databases, and can be used as input for methods of predicting virological response on therapy.

INCREASING PREVALENCE OF TRIPLE-CLASS EXPERIENCED PATIENTS AT 6 US SITES: DATA FROM THE CNICS (CFAR NETWORK OF INTEGRATED CLINICAL SYSTEMS) COHORT

S Jain[1], C Mathews[1], M Saag[2], M Kitahata[3], B Rodriguez[4], J Kahn[5], S Boswell[6], WB Lober[3], M Lederman[4], S Sun[1], S Frost[1], RH Haubrich[1], and the CNICS Study Team

[1]University of California San Diego, San Diego, United States , [2]University of Alabama, Birmingham, United States, [3]University of Washington, Seattle, United States, [4]Case Western Reserve University, Cleveland, United States, [5]University of California San Francisco, San Francisco, United States, [6]Fenway Community Health/Harvard Medical School, Boston, United States.

BACKGROUND: The prevalence of triple-class experienced patients is not clearly defined, and estimates have varied between studies. Estimates are important to evaluate the need for new classes of agents currently in development.

METHODS: Six US CFAR sites contributed data to CNICS from unique point-of-care electronic medical record systems. Three-class exposure was defined as treatment with >=2 NRTI, >=1 NNRTI, and >=2 PI. 95% confidence intervals (95%CI) were calculated by site and at 4 time-points (12/31/2000, 12/31/2002, 12/31/2004, 12/31/2006). Two groups were studied: 1) all cohort patients and 2) the subset on ARV. Patients were considered in the cohort at each time point if at least one visit within (-180, 180) days. HIV RNA (nearest value within 90 days of 4 time-points) evaluated for virologic failure (VF, >200 copies/mL). Site-specific differences and VF were compared via chi-squared statistics.

RESULTS: At the 4 time-points, 2000-2006, there were 3048, 4056, 4892, and 4591 patients in the cohort. The percentages of total patients who had three-class exposure at each time-point were 16.27%[16.26%,16.28%], 18.32%[18.31%,18.33%], 21.87%[21.87%,21.88%], and 25.75%[25.74%,25.75%].

At each two-year time-point, the total numbers of patients on an ARV regimen were 1720, 2269, 2968, and 1977. The percentages of patients on ARV who had three-class exposure at each time-point were 22.56% [22.54%, 22.58%], 25.91% [25.90%, 25.93%], 30.09% [30.07%, 30.10%], and 32.98% [32.96%, 33.00%]. Differences between sites were consistently observed (P <0.0001), but trends in prevalence were consistent across the six sites.

While the percentage of triple-class exposure increased, VF decreased. Prevalence of VF for patients on ARV with/without triple-class exposure were: 2000- 56%[51%, 61%] vs 37%[34%, 40%], 2002- 48%[44%, 52%] vs 32%[30%, 34%], 2004- 37%[34%, 40%] vs 24%[22%, 26%], 2006- 29%[25%, 33%] vs 21%[19%, 23%] (P<0.001 with/without exposure at all time-points).

CONCLUSIONS: Over the past six years, there was a >10% increase in three-class experienced patients both among all patients and among those on therapy, but VF was decreasing. Sensitivity analysis indicated that trends were consistent across the 6 CNICS sites. New classes of ARV medications in development should improve treatment for the growing population of experienced patients in US clinics.

CRN – J. Richard Landis, PhD

PENN 'RE-ENGINEERING THE CLINICAL RESEARCH ENTERPRISE ROADMAP PROGRAM": CHALLENGES OF ADAPTING ORACLE PHARMACEUTICAL APPLICATION FOR USE IN ACADEMIC MEDICAL CENTER RESEARCH

C Helker[1], S Durborow[1], J Dattilo[1], T Chai[1], T Church[1], M Bigliardo[1], J R Landis[2]

[1]Center for Clinical Epidemiology and Biostatistics (CCEB), Clinical Research Computing Unit (CRCU), [2]University of Pennsylvania School of Medicine, Philadelphia, PA

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BACKGROUND: Oracle Clinical is a comprehensive 21 CFR Part 11-compliant data management system designed specifically to meet the needs of the pharmaceutical industry and has grown to be one of the most widely used data management solutions today. Through the NIH's Roadmap grant and a partnership with Oracle Corporation, the University of Pennsylvania acquired software licensing for Oracle Clinical (OC) and Oracle Remote Data Capture (RDC), for pilot use in the academic medical center (AMC) environment.

Workflow and resource models differ significantly between the pharmaceutical industry and academic medical centers. For example, in the AMC model, clinical site personnel are relied upon to code adverse events and concomitant medications, however, in the industry model coding is completed by a specialist at the sponsor company. The University's Roadmap team's objective was to evaluate the functionality of OC and RDC and engineer necessary modifications to effectively execute a randomized clinical trial, utilizing remote data entry, in accordance with the academic research model.

METHODS: The University's Roadmap team chose to pilot the software for a Phase II, randomized, partially blinded, Ophthalmology clinical trial, requiring onsite data entry at 50 sites, and the establishment of an Ophthalmology Coordinating Center (OCC) responsible for site and data management. The disparity in work flow and resource models led to significant challenges in adapting the tools for use in this trial and the team worked with Oracle Corporation consultant's to develop customized solutions.

Procedures for dynamically randomizing subjects and maintaining partial blinding at the clinical sites were designed. Access to a variety of informatics tools was enhanced to make usage at clinical sites more intuitive and to provide functionality not available in RDC. The process for reporting and coding adverse events and concomitant medications was adapted to effectively interact with OC and RDC. Also, in an effort to facilitate remote monitoring, custom user roles were created to enable appropriate data access and update privileges at the clinical sites, in conjunction with extensive edit check and custom validation procedures.

RESULTS: The University's Roadmap team was able to adapt the configuration of OC and RDC to create a comprehensive data management system which met the needs of the OCC in terms of data and site management, relative to resources and workflow requirements. The system is also an intuitive, user friendly configuration for the clinical sites, which employ staff with varied levels of research experience. The challenges encountered while designing compromises resulted in the team acquiring a far greater understanding of the application and its functionality, beyond what is normally outlined in formal training sessions or manuals.

CONCLUSIONS: Oracle Clinical and Remote Data Capture are very powerful, effective tools; however, they require customization to accommodate academic medical center resource and workflow requirements. Additional beneficial features of these tools are the ability to efficiently copy complete data modules, easily creating new studies, in a 21 CFR Part 11-compliant environment, and the interoperability and standardization it will promote.

PENN 'RE-ENGINEERING THE CLINICAL RESEARCH ENTERPRISE ROADMAP PROGRAM': STANDARDIZATION INITIATIVE FOR CLINICAL TRIALS SITE MONITORING ACROSS THE UNIVERSITY OF PENNSYLVANIA CLINICAL RESEARCH ENTERPRISE

R Madigan[2], D Cifelli[2], G Fromell[1]

[1]Office of Human Research (OHR), [2]Center for Clinical Epidemiology and Biostatistics (CCEB), Clinical Research Computing Unit (CRCU), University of Pennsylvania School of Medicine, Philadelphia, PA

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BACKGROUND: Developing and implementing standardized procedures for monitoring the conduct and documentation of clinical research is integral to ensuring responsible conduct of clinical research, GCP compliance, and quality management. Clinical site monitoring, however, is considered to be one of the most time consuming and labor intensive tasks in clinical trial management. As part of the University of Pennsylvania Academic Medical Center enterprise-wide Clinical Research Informatics (CRI) standards program, the Office of Human Research (OHR) and the Coordinating Center NIH Roadmap team developed a research site monitoring initiative for use in supporting clinical research processes and performance within the Penn clinical research organization and the coordinating center multi-site research projects.

METHODS: Existing responsibilities and primary tasks of clinical research coordinators and project managers were examined as well as training needs, to determine the feasibility of having this group conduct formal site monitoring activities of studies for which they are not directly responsible, or in the case of the coordinating center, studies coordinated in multi-site locations. Organized as a component of the Penn Office of Human Research Oversight and Quality Assurance Program, the tools and educational materials for this comprehensive site monitoring initiative were developed for on-line and class room training to teach Penn research coordinators and project managers how to systematically monitor clinical trails.

RESULTS: Collaborative review and testing of the instructional prototype indicates that this initiative provides sufficient model guidelines and best practices to support implementing standardized clinical trial monitoring at a full scale level.

CONCLUSIONS: Although the impact of this initiative on quality improvement, research management, and cost effectiveness remains to be evaluated, we believe that the value of standardized monitoring of clinical trials performance and compliance will be transformative. Such an initiative will also inform the development of well-designed tools to support clinical research workflow.

PENN 'RE-ENGINEERING THE CLINICAL RESEARCH ENTERPRISE ROADMAP PROGRAM': STANDARDIZATION INITIATIVE FOR CLINICAL TRIALS INFORMATICS TOOLS AND DATA STANDARDS

S Durborow[1], C. Helker[1], M Bigliardo[1], J Dattilo[1], T Chai[1], T Church[1], J R Landis[2]

[1]Office of Human Research (OHR), [2]Center for Clinical Epidemiology and Biostatistics (CCEB), University of Pennsylvania School of Medicine, Philadelphia, PA

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BACKGROUND: Clinical research at the University of Pennsylvania, like many academic medical institutions, is performed by a variety of investigators with an even greater variety of scientific interests. Most research studies conducted at the university are supported by grant funding from government and industry sponsors. These sponsors often have specific requirements concerning measures that should be taken to insure data quality. Many times they do not. The result of such varied requirements is the development of silos of technology and expertise where each group conducts studies their own way. While plenty of sound, important research is completed by these many groups, challenges exist in comparing results between studies and across disease areas. In addition, informatics tools to manage study data are not consistent across research groups and thereby leave such issues as data security and data quality open to question.

METHODS: The University of Pennsylvania, through the NIH's Roadmap grant, looked to provide a standardized solution to informatics tools for conducting clinical research as well as to identify and implement standards for data collection associated with research efforts. Partnering with Oracle Corporation, the University's Roadmap project team licensed and installed Oracle's Pharmaceutical Applications suite of tools which includes Oracle Clinical. Oracle Clinical is a data collection and management tool that includes an object library structure meant to contain reusable study elements such as case report forms. In order to make this library applicable to many clinical studies, the Roadmap team incorporated emerging standards from CDISC into new clinical study development. In addition, the efforts that NCI's CaBIG initiative had spent were leveraged to gain a head start on populating the Oracle Clinical library with data elements that have been vetted through that public forum. The Roadmap project team then identified seven clinical studies from four different departments to pilot their development using the data standards and Oracle Clinical.

RESULTS: The team was able to successfully create and conduct the studies to the satisfaction of the investigators. Three of the seven studies were related and the team was able to successfully demonstrate the benefits of data element reusability for rapid development and consistent data quality safeguards.

CONCLUSIONS: Oracle Clinical has been in use in the pharmaceutical industry for many years; however, the application of this tool for academic medical research is not common. Employing a tool such as Oracle Clinical at Penn allows the School of Medicine to work toward promoting more standards in clinical research data management and provides individual researchers with informatics tools to help conduct trials more compatibly with other studies.

PENN 'RE-ENGINEERING THE CLINICAL RESEARCH ENTERPRISE ROADMAP PROGRAM': DEVELOPING AND INTEGRATING A SYSTEMS SECURITY PLAN TO SUPPORT ACADEMIC MEDICAL AND INDUSTRY SPONSORED CLINICAL RESEARCH NETWORK ARCHITECTURE

J L Kaylor[1], R R Godshall[1], R Madigan[1], J R Landis[2]

[1]Clinical Research Computing Unit (CRCU), [2]Center for Clinical Epidemiology and Biostatistics (CCEB), University of Pennsylvania School of Medicine, Philadelphia, PA

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BACKGROUND: Developing, Implementing, and Managing an effective security program across a broad Clinical Research computing spectrum has always been a high priority initiative. With HIPAA privacy and security regulations now well established, and FISMA standards, guidelines and information now pervasively being promoted across the federal research programs; methodologies and operational frameworks are needed to help guide and ensure that appropriate IT processes used in research are implemented and that usage of standard security controls and measurements continues on an ongoing basis.

METHODS: Through a funding stream in the Roadmap program, a pre-FISMA security plan was developed and refined over several years within the CCEB. This security plan is now in a redesign, specifically to address the FISMA control categories and standards being promoted. In order to provide a framework for the IT operational staff in implementing the various controls within FISMA, the CCEB has implemented an IT governance framework, i.e. CobiT, to be used to ensure the objectives, maturity and continuity of the overall security program can be managed and reported. The overall security program will be guided by an IT governance framework. Within this governance framework, various cross reference mapping documents will be used to establish links between the governance objectives and the operational security controls objects. This configuration is considered essential to provide a lineage between the operational processes and the procedural reporting needed for HIPAA, FISMA, and management overview.

RESULTS: The initial cross reference mappings are still being completed and the IT governance model is currently being introduced across the Research Computing environment. The CCEB IT operations unit has implemented a gap analysis of its security plan as an effective FISMA oriented security plan via an external audit firm and the formal review has resulted in a remediation plan containing only minor exceptions. This indicates our initial success with the security plan format and the operational processes currently in place. Although the maturity level of the security path and the linking IT governance plan is still new, due to inexperience with this new format, results from the gap analysis indicate a level of compliance on par with FISMA ATO requirements.

CONCLUSIONS: Although the CCEB IT operational unit is within an academic medical setting, the use of an IT Governance framework linked via mapping documents to IT operational standards has allowed this unit to provide to the federal government results effectively equal to an ATO (authority to operate). In doing so, procedures can be routinized as an ongoing part of the IT operational process, allowing reporting and monitoring to have the appropriate links to ensure compliance is not just a paper activity, but based on verified/verifiable daily IT process completions.

HMORN – CCSN – Eric Larson, MD, MPH

KEY ACCOMPLISHMENTS, TOOLS AND RESOURCES OF THE CCSN

Eric B Larson MD, MPH and Sarah M Greene MPH

BACKGROUND: The Coordinated Clinical Studies Network (CCSN) has created tools and informational materials to facilitate multi-center collaborations and infrastructure development across the HMO Research Network (HMORN). These resources are geared toward the most common but potentially challenging aspects of multi-site studies, such as recruitment, IRB review, and data acquisition. As such, they are adaptable to a range of content areas, including those in which our HMORN investigators have active projects, cancer, cardiovascular, drug effectiveness and vaccine safety, and those in more formative stages, such as diabetes and aging.

METHODS: We developed these comprehensive resources by building from existing tools in currently-funded multi-center studies, and addressing concrete suggestions from Investigators, Project Managers, and Administrators via a web-based survey, formal meeting discussions, and informal conversations. Our dissemination strategies have included web posting, email and listserv communications, HMORN conferences, non-HMORN conferences, and staff seminars. Our presentation will list tools and resources created and describe the purpose of each, including procedures for conducting facilitated IRB review for low risk multi-site projects, data use agreement toolkit, cluster randomized trial guide, recommendations for increasing cardiologist participation in clinical trials, research administration and budget development tools, and more.

RESULTS: Key accomplishments of the CCSN include (1) shifts in thinking, both locally and nationally, in terms of the intellectual capital, research capacity and unique potential of the HMORN; (2) infrastructure developments, tool and resources aimed at reducing barriers to conducting multi-site research within the HMORN; and (3) the enduring legacy of the CCSN's accomplishments on the culture and organization of the HMORN.

CONCLUSIONS: The lessons, tools and resources of the CCSN can be translated to other research partnerships that aim to efficiently and effectively carry our multi-institutional research projects. Capacity-building takes time and commitment, but has been a worthwhile investment that will continue to pay dividends over time as new consortia are developed. HMORN sites involved in funded CTSA programs are adapting a variety of these resources for new research networks and partnerships.

CRITICAL CARE DECISIONS – Alan Morris, MD

REENGINEERING CLINICAL RESEARCH IN CRITICAL CARE

AH Morris[1], T Thompson, G Bernard, R Brower, D Willson, D Levin, D Schoenfeld, A Randolph.

[1]University of Utah/LDS Hospital, Utah

OBJECTIVE: To evaluate the feasibility of developing, refining, and exporting an adequately explicit decision-support tool that standardizes clinician decision-making. To link the activities of disparate clinical research networks.

METHODS: We used informatics, recruitment and retention, and/or training approaches. We convened a group of 27 intensive care unit (ICU) sites, half pediatric and half adult, in 3 countries on 2 continents. We developed and refined a bedside computerized protocol that standardized clinician decisions regarding insulin treatment to control blood sugar (eProtocol-insulin). Members of 3 research networks, the NHLBI Adult Respiratory Distress Syndrome (ARDS) Network, the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, and the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN) attend each other's meetings.

RESULTS: eProtocol-insulin was initially developed and validated at LDS Hospital. It was then exported to several adult and pediatric ICUs and further refined. eProtocol-insulin has generated 33,405 patient-tailored therapy instructions (96% accepted) in 802 adult ICU patients and 16,611 patient-tailored instructions (90% accepted) in 222 pediatric ICU patients. Safety was established (about 0.1% blood sugars ≤40 mg/dl). Members of the 3 research networks have attended other network meetings and have participated in common project development and execution.

CONCLUSIONS: We have successfully developed and distributed a common replicable bedside computerized decision-support tool for blood glucose control (eProtocol-insulin) for adults and children. This tool has bridged the disciplines of Pediatrics and Internal Medicine. We have linked effectively the 3 research networks. The advent of tools that can enable clinicians to make consistent evidence-based decisions has broad implications for clinical research, clinical practice, and health care policy.

BLOOD GLUCOSE CONTROL WITH THREE DIFFERENT QI STRATEGIES.

J Truwit[1], J Steingrub, J Orme Jr, KH Lee, M Tidswell, TY Leong, G Li, E Hirshberg, D Sorenson, H Warner, K Sward, AH Morris, MD

[1]University of Virginia Health System, Charlottesville, VA

OBJECTIVE: Guidelines and protocols (both paper-based and computer) are used to stabilize clinical care process. Clinicians manage blood glucose in ICU patients because patient survival may increase 6-9% absolute/10 mg/dl reductions in blood glucose.

METHODS: We compared three 80-110 mg/dl blood glucose target decision-support strategies with varying detail and process control: a simple guideline, (without a bedside tool), a bedside paper-based protocol, and a bedside computer protocol.

3 Strategies	Observations	Patients	80-110	%<40	Mean	Med	Mode	IQ Range		SD
Computer	19,480	492	46%	.08	113	105	93	89	126	41
Paper	21,599	-	28%	.04	134	124	114	102	154	49
Guideline	3,557	87	22%	.2	141	133	120	109	163	49

RESULTS: Glucose values were lowest and variation (SD) least with the computer protocol, and highest with the simple guideline. The paper-based protocol was inter-mediate. We distributed the computer protocol to three different clinical sites (2 in the USA and 1 in Singapore). Blood glucose mean, median, and mode were indistinguishable among the Asian and US computerized protocol sites. Bedside clinician compliance with protocol instructions was 95-98%.

Computer	Observations	Patients	80-110	%<40	Mean	Median	Mode	Clinician Compliance
LDS Hosp	19,480	275	46%	0.08	113	105	93	95%
U Virginia	2,250	~28	42%	0.18	116	106	100	95%
Singapore	11,282	492	41%	0.66	111	103	98	98%

CONCLUSIONS: Blood glucose is lower with computerized protocols. The computerized protocol enabled a replicable means of process control in three sites in two cultural environments. Replicable methodology has important implications for clinical research and practice, and for healthcare policy.

REASONS FOR DECLINING INSTRUCTIONS FROM A COMPUTER-BASED INSULIN PROTOCOL

K Sward[1], J Orme Jr., D Sorenson, H Warner, AH Morris
[1]University of Utah

PURPOSE: To describe reasons for which clinicians decline computer-based insulin titration protocol recommendations.

METHODS: We performed an exploratory, correlational, study of data from subjects enrolled in a clinical validation of an adequately explicit computer protocol. We used a computer-based insulin titration protocol (eProtocol-insulin) to standardize bedside clinician decision-making for a multi-site, adult and pediatric clinical study. Clinicians accepted the recommendations from the protocol 93% of the time. When clinicians declined eProtocol-insulin recommendations they indicated the reasons for declining. We conducted a content analysis of those free-text reasons for declining recommendations.

Reason	Overall	Adult	Pediatric
Clinician Opinion	64.3%	47.7%	81.5%
Software issues	15.7%	31.0%	7.3%
Barriers	8.2%	11.1%	5.2%
No reason given	7.9%	11.1%	4.7%
Incorrect data	4.6%	7.2%	1.9%
Miscellaneous	0.3%	0.2%	0.5%

RESULTS: 93% of 12,893 instructions were accepted. Bedside clinicians declined 5% of instructions in adult patients, and 9% of instructions in pediatric patients. The most common reason to decline recommendations was clinician opinion (81.5% of pediatric patient declined instructions, and 47.7% of adult patient declined instructions). The basis for opposing clinician opinions included data not available to the computer protocol, perceived patient data trends, and unspecified

disagreement. The second most common reason for declining was linked to software issues; the primary software issue was our failure to allow a clinician to enter glucose values but not get a new insulin instruction (e.g., back charting glucose values obtained when the patient was out of the intensive care unit). Less common reasons included malfunctioning intravenous lines and insulin not available from the pharmacy. Incorrect data, and miscellaneous reasons (e.g., the nurse's responding to emergencies with other patients) accounted for less than 5% of the overall declines. No reason was given for 7.9% of declined recommendations overall.

IMPLICATIONS FOR POLICY/PRACTICE: Computerized protocols can improve the rigor of research and quality improvement studies. Medical knowledge is not static, and the knowledge base (rules) within a computer-based protocol should be continuously evaluated. Capturing clinician compliance and reasons for declining protocol recommendations at the point of care provides a realistic picture of protocol acceptance. Evaluating reasons for declining protocol recommendations can suggest areas for potential software and/or knowledge base refinement.

NIH (HHSN268200425210C)

ePROTOCOL-INSULIN DEVELOPMENT AND REFINEMENT IN TWO RESEARCH NETWORKS

T Thompson[1], J Orme, R Brower, G Bernard, J Truwit, D Willson, D Hite, J Lacroix, V Nadkarni, P Luckett, N Thomas, A Zaritsky, C Bogue, J Steingrub, V Srinivasen, M Tidswell, E Hirshberg, C Grissom, L Jefferson, A Randolph, AH Morris

[1]Massachusetts General Hospital, Pulmonary Critical Care Unit, Boston, Mass

OBJECTIVE: Interoperable tools must be effective and generalizable to multiple research networks. We developed a computerized protocol (eProtocol-insulin) for the control of blood glucose with IV insulin in multiple institutions, two disciplines, and two research networks. We chose a blood glucose range of 80-110 mg/dl for the participating adult and pediatric ICUs because of reports of increased survival with an 80-110 mg/dl blood glucose target.

METHODS: We used Information Technology and Network Operations techniques. We developed a computerized intravenous insulin algorithm to control blood sugar in adult and pediatric patients. A multi-institutional group of adult and pediatric intensivists from two different research networks evaluated an early version eProtocol-insulin (v3) developed at LDS Hospital in Utah. First, we analyzed its performance with clinically relevant ranges of blood glucose, insulin infusion rates, and changes in blood glucose. Second, we reviewed patients managed with eProtocol-insulin at LDS. Third, we reviewed frequency distributions of eProtocol-insulin blood glucose measurements. Fourth, we developed 219 clinical simulations for a range of blood glucose values, rates of glucose change, and insulin infusions. We compared eProtocol-insulin clinical simulation instructions to those of 6 experienced ICU physicians.

RESULTS: The majority of eProtocol-insulin (v3) instructions were deemed to be reasonable after the four-step multi-instutional group review. Modest refinements (v4) were re-reviewed and introduced into clinical practice:

Version	Number of Glucose measurements	Mean glucose mg/dl	SD	% Within 80-110 mg/dl	%<=40 mg/dl
3	10,367	113	48	44.2	0.106
4	13,017	112	40	45.9	0.084

Our hypoglycemia rate (%<=40 mg/dl) with eProtocol-insulin was low compared to published ICU rates.

CONCLUSIONS: We successfully used a multicenter, two-network (pediatric and adult) collaboration to develop refine and disseminate an explicit, computerized, bedside decision support protocol.

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FRAME-BASED TOOLS FOR POINT-OF–CARE COMPUTERIZED PROTOCOLS.

D Sorenson[1], AH Morris, H Warner, K Sward J Orme, T Clemmer.
[1]University of Utah

INTRODUCTION: Bedside computerized protocols using adequately-explicit detail ensure replicability and reduce clinical errors due to variation in medical decision-making. Developing and refining such computerized protocols requires extensive effort using a process called knowledge engineering. We have developed a frame-based software tool for rapidly developing, refining, and implementing computerized protocols.

METHODS: Using an application called FrameBuilder, knowledge is represented as frames, which are comprised of a title, a list of patient findings (and/or subframes), and a logic statement. Each frame generates a value (0 to 1 for Boolean logic or a numerical value for a mathematical calculation). Each frame can have additional “if-then” logic to interpret or validate the result. Any patient finding (or frame) will drive all related decisions and queries necessary to make a final decision (e.g., bedside protocol instruction). Frames can also run database queries, generate instructions, generate dialogs, and make changes to the user interface. FrameBuilder uses a FrameEditor to create frames, queries, instructions, and user dialogs. These data, along with a data dictionary, are generated automatically in an associated database and constitute the knowledge base. No programming is necessary by the knowledge engineer, thereby allowing clinicians to be involved directly in the knowledge engineering process. A FormEditor creates data entry screens with built-in validation of entered data. Patient data entered by the user on the data entry screen are stored in the database, initiate evaluation of appropriate frames and queries of previous data, and generate clinician instructions (which can be accepted or declined). A built-in rules engine evaluates the individual frames and the decision hierarchy comprised of the frame results. Automatic batch processing of multiple patient data sets enables rapid testing of protocol logic. All knowledge engineering features can be turned off, leaving a fully functional bedside decision support application that will run on any PC using a Windows operating system.

RESULTS: The frame-based tool has increased the speed of clinical knowledge capture, protocol rule development, rule testing, and implementation of bedside decision support applications. The tool has created three clinical applications and two have been clinically tested and implemented.

CONCLUSIONS: The frame-based tool set streamlines clinical coordinator form, data transfer, and protocol rule development and refinement and reduces the time to implementation of computerized clinical protocols.

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VALIDATED ADEQUATELY EXPLICIT COMPUTER PROTOCOLS TO BE USED FOR REPLICABLE QI STUDIES

L Savitz[1], AH Morris, K Sward, J Orme, T Clemmer.

[1]University of Utah/LDS Hospital, Intermountain Medical Center, Sorenson Heart and Lung Center, Murray, Utah

PURPOSE: To use the replicable methods developed for Randomized Clinical Trials as tools for large-scale Quality Improvement studies. This will take advantage of the resources invested in development of adequately explicit computer protocols that enable replicable clinical trail experimental methods. These adequately explicit protocols have already been exported to the clinical care environment and used successfully to standardize clinician decision-making in usual clinical care within Intermountain Healthcare.

RESEARCH DESIGN: Demonstration of research computer protocols to effect translation to Quality Improvement studies.

STUDY POPULATION/SAMPLE: Patients supported with computer protocols implemented in usual care systems, such as Intermountain Healthcare's electronic medical system for usual clinical care.

DATA SOURCE(S): Electronic clinical data stored in the adequately explicit computer protocol application and in the electronic medical record.

METHODS: We have used validated and successfully implemented randomized controlled clinical trial adequately explicit computer protocols for translation to usual clinical care. We will use these protocols for subsequent quality improvement studies.

RESULTS: Validated adequately explicit research computer protocols for mechanical ventilation and blood glucose management were installed in the Intermountain Healthcare electronic medical system. Mechanical ventilation and blood glucose control have been carried out with these protocols as part of usual clinical care. Data in the electronic medical record associated with use of these computer protocols are now available for quality improvement studies

IMPLICATIONS FOR POLICY/PRACTICE: We translated replicable methods successfully from research projects such as randomized controlled clinical trials for usual clinical care use. This translation represents an opportunity to conduct rigorous quality improvement studies with the same computer protocol methods. This should be of interest to policy makers in the healthcare community and to quality improvement researchers in practice.

NIH (HHSN268200425210C)

EPCRN – Kevin Peterson, MD

THE ELECTRONIC PRIMARY CARE RESEARCH NETWORK (ePCRN): A NEW ERA IN PRIMARY CARE PRACTICE-BASED RESEARCH (ePCRN 1)

Peterson K, Delaney B, Arvanitis T, Taweel A, Speedie S, Sims I, Fontaine P

BACKGROUND: In order to accelerate the translation of clinical research into practice, new partnerships with primary care providers who deliver the majority of care to the US population need to be developed. These partnerships should enhance the ability of investigators to conduct research, as well as facilitate the delivery to clinicians of better tools to provide care. Although potentially rich sources of patients and data, community primary care practices have not traditionally been sites for clinical research. Reasons for this include difficulty identifying subjects, delivery of complex interventions, privacy/confidentiality restrictions, and competing demands within community practices. Using emerging technologies to facilitate accepted Practice-Based Research Network (PBRN) methodologies, the ePCRN provides primary care practices throughout the US with an electronic architecture compatible with most electronic health records (EHRs) that overcomes these obstacles. Introduced to primary care physicians through the Federation of Practice-Based Research Networks (FPBRN), an organization of over 8,000 primary care physicians in over 2,700 practices, the ePCRN uses advanced Grid technology to enhance clinical research and translation in wide variety of primary care settings. The ePCRN architecture provides PBRN directors, clinical research organizations, and clinical translational science centers with a sophisticated solution for integrating primary physicians and their practice populations into the academic clinical research enterprise.

METHODS: The ePCRN uses the nationally standardized CCD/CCR export from CCHIT approved electronic health records (EHR) to create a standardized registry containing XML strings. This dataset acts as a "gateway" using PKI certificates to accept SQL queries from the ePCRN "portal" through a Globus OGSA-DAI framework. The registries form a virtual distributed dataset among participating community practices with all requests filtered through the regional PBRN Research Director. The database is never centralized, and medical data remains at the local practice and under control of the local EHR provider. The registry supports a local JAVA application that provides measures of practice and provider performance, patient specific profiles, and eligibility for specific research projects. The regional PBRN director negotiates allowable searches, and provides research and additional quality improvement support for the practice. Practices can elect to only receive eligibility information and clinical alerts (no data sharing), or to push anonomyzed data, and/or private health data for research studies in which the practice has agreed to participate and where either patient consent has been obtained or transfer of information meets local study specific IRB permissions and limitations.

RESULTS: The principle advantage to the researcher is the identification and recruitment of patients in community practices that are eligible for clinical research studies, and the enabling of data collection from consented subjects or from limited data sets. Reciprocally, the community practice is provided with tools that measure quality of care, improve the integration of new research findings, and allow primary care providers and patients to participate in clinical research without compromising local resources or confidentiality. The ePCRN portal additionally provides a variety of new research tools designed specifically for primary care PBRNs based upon the newly defined Primary Care Research Object Model (PCROM). These tools allow more rapid research design and greater standardization of data elements and case report forms through integration of the Enterprise Vocabulary

System (EVS) and data structured repository (DSR) developed by the Cancer Bioinformatics Grid. These facilities form important elements of a PBRN clinical trial information system currently underway.

CONCLUSIONS: The ePCRN provides a model for both electronic integration and governance that promotes the successful involvement of community practice-based research activities with academic clinical research and translation centers. As electronic health records are more widely adopted in primary care, the ePCRN will help to define a new era for primary care clinical research.

ACKNOWLEDGMENTS: The ePCRN gratefully acknowledges the contributions of Carol Lange, Mark Janowiec, Lei Zhao, Joseph Stone, Mike Schendel, and the members and staff of the following PBRNs:

THE PRIMARY CARE RESEARCH OBJECT MODEL (PCROM): A COMPUTABLE INFORMATION MODEL FOR PRACTICE-BASED PRIMARY CARE RESEARCH (ePCRN 2)

Speedie S, Taweel A, Sim I, Arvanitis T, Delaney B, Peterson K, Fontaine P

BACKGROUND: The organization and management of clinical research performed in a community primary care practice differs substantially from that used in other clinical research settings. Information systems designed to support primary care practice-based research must account for workflow, resources, and research roles that do not resemble those commonly found in academic centers or contract research organizations. With the rapid growth of practice-based research networks, it is necessary to have a model of the research process that is standardized and computable in order to promote interoperability with other clinical systems.

DESIGN: A UML modeling process was undertaken to develop use cases, activity diagrams and a class model that captured fundamental components of practice-based clinical research conducted in a primary care setting. The initial scope of the primary care research object model (PCROM) was to provide a standardized representation of activities necessary for performance of a randomized clinical trial (RCT). The PCROM was evaluated and validated by domain experts from across the world, and underwent a detailed comparison with the RCRIM (HL7), CTOM (CDISC), and BRIDG (NCI) reference models for regulated clinical research

RESULTS: A set of class definitions and a class diagram are presented that capture the fundamental components of a practice-based primary care RCT. Although 81% of PCROM objects mapped in some fashion to the BRIDG reference model, some variation existed in class and subclass assignment,. Some PCROM components were incomplete, or missing entirely from existing models.

CONCLUSION: The PCROM represents an important link between existing reference models for clinical research and the real-world design and implementation of information systems that support the design, execution, and analysis of practice-based primary care clinical trials. Although the high degree of correspondence between PCROM and existing Research Object Models provides evidence for validity and comprehensiveness of existing models, implementation of clinical research in a primary care setting requires modification of some objects Implementation of PCROM standards into computable interfaces will promote both interoperability and efficiency of primary care research.

SECURE DISTRIBUTED SEARCHES OF ELECTRONIC HEALTH RECORDS TO FIND ELIGIBLE SUBJECTS FOR RANDOMIZED CONTROLLED TRIALS IN PRIMARY CARE (ePCRN 3)

Delaney B, Taweel A, Peterson K, Arvanitis T, Speedie S, Janowiec M., Sim I, Hobbs R

BACKGROUND: One of the principal tasks for completing a randomized controlled trial (RCT) successfully is to actually recruit the required number of participants. For RCTs that will recruit from a pool of prevalent cases, it is possible to conduct searches of individual electronic health records (eHRs) held in clinics, but this is a laborious process, and results may not be comparable between systems. The electronic Primary Care Research Network (ePCRN) is an NIH Roadmap funded project designed to construct of an electronic platform for conducting clinical trials in primary care.

OBJECTIVE: To develop a tool, as part of an overall clinical trial management system, to capture eligibility criteria for an RCT and enable a distributed, secure search of electronic health records in order to identify eligible participants. The tool should have an intuitive user interface that links to the National Cancer Institute's (NCI) Enterprise Vocabulary Services (EVS), which provide a reference medical terminology vocabulary and standard common data elements.

METHOD: The developed tool provides a dynamic flexible graphical interface to identify clinical concepts, e.g. clinical problems, lab tests etc., and allow searching and importing them directly from NCI EVS on-line servers and databases. Each of these concepts is coded with several coding systems, such as SNOMED, ICD9, etc. Several codes are incorporated for each concept to allow greater searching flexibility and interoperability across Electronic Healthcare Records (EHRs) that are used in order to identify and recruit potential trial subjects. The interface provides dynamic panes for six generic concepts, namely age, gender, clinical problems, Lab Tests, Vital Signs and Drugs. Specific concepts under each of these six categories can be dynamically added or removed and combined with other concepts, as per the eligibility criteria rules, in several supported logical combinations. Because the tool is directly connected to the EVS system, through the appropriate Application Programming Interfaces (APIs), any changes and additions in the EVS terminology pool are reflected in the eligibility criteria concept model.

RESULTS: Once an eligibility criterion is captured, it can be saved and mapped into several standard Internet metadata representation formats, including XML, xPath or SQL. The tool uses these formats to submit generated queries to remote EHRs and thus enabling the conduct feasibility studies for potential trials. Counts of eligibility subjects per clinic or research network that meet the submitted query conditions are returned as a result. Using a 'clinic gateway' and the CCR export standard, the tool can then be used to flag eligible subjects in the EHR, allowing the clinic staff to contact the subject for recruitment.

CONCLUSIONS: The ePCRN eligibility tool can capture RCT eligibility criteria with standard codes and clinical concepts using the thesaurus and metathesaurus facilities of the NCI's EVS, and identify eligible participants for the trials. It has the potential to greatly enhance the availability of primary care to research, by decreasing the cost and effort of obtaining access to subjects, whilst maintaining appropriate confidentiality and security.

ePCRN – Kevin Peterson, MD

A SECURE FEDERATED HEALTH DATA QUERY SYSTEM FOR PRIMARY CARE CLINICAL TRIALS ON THE GRID (ePCRN 4)

Peterson K, Weissman J, Kim S, Kim J

BACKGROUND: The ePCRN (electronic Primary Care Research Network) is an infrastructure that allows primary care practices to link with researchers conducting clinical research. The ePCRN provides electronic access to standard vocabularies (EVS), conceptual modeling of clinical trials and clinical trials management tools in the primary care domain through sophisticated research portals. To support the linkage between community practices and these research portals, a need existed to develop a standards-based distributed data query middleware system to enable secure eligibility identification for clinical trials

DESIGN: The ePCRN query architecture consists of the following interactions: registering, discovering, and querying databases in the clinics that can be accessed via Grid services interfaces. A middleware OGSA-DAI (Open Grid Service Architecture – Data Access & Integration, www.ogsadai.org.uk) is adopted to allow data resources, such as relational or XML databases to be exposed as Grid services. This OGSA-DAI data service is deployed in the default Globus Toolkit WSRF-compliant Web Services Core java container (www.globus.org). In order to support a Web-based distributed directory service (publishing/discovering Web services) for the OGSA-DAI services, we adopt Apache jUDDI (ws.apache.org/juddi), an open source java implementation of UDDI (Universal, Description, Discovery, and Integration) specification. Client APIs supporting jUDDI publish/query, concurrent distributed queries, and error/exception handling were developed.

RESULTS: The overall ePCRN security model adopts a “defense-in-depth” strategy. The ePCRN security framework is based on a X.509 PKI-based security scheme. It supports mutual authentication between clients and services, TLS (Transport Level Security)-based secure communication, and authorization (access control). Each XML clinic-level database is exposed to the Web as a SOAP-based Grid service using OGSA-DAI on top of the Globus Toolkit infrastructure, the de facto open source grid standard. For secured communication, both server and client side require credentials (certificate and key) and a proxy for TLS based communication. During the handshaking process, proxy certificates are exchanged as well as client/server’s public key to test each party’s authenticity. If this handshaking succeeds, a TLS based secure session is set up and all SOAP (Simple Object Access Protocol, www.w3.org/TR/soap) messages are encrypted and transferred securely. For access control to services, data resources, and database activities, each user is associated with a specific and identifiable ePCRN role that is allocated a set of privileges, controlled by the local clinic site. There are three different tiers for authorization and access control: 1) user-role mapping after authentication, 2) access control on resources and activities, and 3) access control on database layer.

CONCLUSIONS: The system enables distributed queries to be committed concurrently on at least 1000 distributed databases holding XML-based Continuity of Care Record exports. The implementation provides highly secure communication while also maximizing scalability by allowing parallel processing of queries at each data site.

IMPROVING COLLABORATION AMONG PRIMARY CARE PRACTICE-BASED RESEARCH NETWORKS USING ACCESS GRID TECHNOLOGY (ePCRN 5)

Nagykaldi Z., Stone J, Peterson K, Janowiec M, Fox C

BACKGROUND: The electronic Primary Care Research Network (ePCRN) allows primary care practices to link with researchers conducting clinical research anywhere in the United States via the Internet. Access Grid (AG) is an emerging Internet-based technology that employs existing or specialized computer hardware to run advanced audiovisual communication software through the high bandwidth connections provided by Internet2. AG provides outstanding audio-visual quality that simulates the experience of face-to-face meetings in an integrated communication environment that greatly enhances virtual collaborations.

METHODS: Although AG has been designed to operate through high-speed Internet connections; it can also be configured to use conventional with little compromise in AV quality. While high-grade commercial group conferencing tools are expensive, AG software is freely available in an open-source solution that incorporates both server and client applications and provides greater flexibility than proprietary software. This flexibility is a key feature for making a communication solution successful in a medical research environment. Current computers are able to handle the latest versions of the Venue Client software (version 2.4 and 3.0) although tightly controlled medical or corporate networks provide significant barriers.

RESULTS: The collaborative meetings during the development of the ePCRN showed that AG technology is a uniquely effective tool for enhancing group collaboration in the virtual space. Areas of improvement included meta-communication (visual cues and body language), face-recognition, group-level interaction and feedback (e.g. voting by raising hands), synchronization of participation (e.g. participants could indicate their intention to speak) that decreases the number of interruptions and ease of communication (e.g. no static noise.)

CONCLUSIONS: Access Grid technology greatly enhances group to group collaboration that is commonly required in PBRN research environments. The ePCRN has demonstrated the feasibility and usefulness of this technology in enhancing the collaboration necessary in primary care research. AG technology has the potential to more effective venues for communication and collaboration in practice based research networking.

MEASURING OUTCOMES OF CLINICAL CONNECTIVITY: THE ELECTRONIC PRIMARY CARE RESEARCH NETWORK'S MOCC TRIAL (ePCRN 6)

Fontaine P, Speedie S, Mendenhall T, Peterson K, Delaney B

BACKGROUND: The electronic Primary Care Research Network (ePCRN) is an expansion of the PBRN concept that links member networks through a common electronic infrastructure. The ePCRN features a secure web portal for online recruitment and consent, real-time computerized randomization, and capability for direct data entry into a centralized database.

The Measuring Outcomes of Clinical Connectivity (MOCC) trial was conceived as a dual-purpose feasibility pilot that would test the ePCRN's capacity to perform under the demands of a randomized controlled trial (RCT) and would recruit PBRN physicians into a

randomized two-armed trial to evaluate optimal procedures for electronic data entry. Results of the MOCC trial would aid in the design of data entry screens and procedures, as well as establish a core of participating members for future RCTs in the ePCRN.

METHODS: Setting and Participants: Members of 10 participating U.S. PBRNs who had completed the ePCRN enrollment and identity verification process were eligible to participate. Members are comprised of primary care physicians, allied health personnel, and PBRN research assistants.

INSTRUMENT: Participants received simulated health information for five simulated patients, formatted either as electronic progress notes ("long form") or in a tabular format ("short form"). The electronic format resembled a typical physician's dictated note. With the tabular format, pertinent information was pre-abstracted from the medical record. Participants were required to enter 50 data elements that included patient demographics, date of visit, weight, blood pressure, hemoglobin A1C and serum creatnine values. Because number and type of data errors were the subject of investigation, the electronic data entry form contained no prompts, pull-down menus, or internal validation checks.

Main Outcome Measures:

1. System performance including peak usage, including log-in time and number of concurrent log-ins, number of attempts required to complete the MOCC trial, number and reasons for any inadvertent disconnections.
2. Physician/research assistant performance including length of time to enter required information, percent of items correctly entered, and types of data-entry errors.

RESULTS: Ten geographically dispersed PBRNs enrolled 100 members and completed the study in less than seven weeks with no problems in system performance. Participants entering data from the short form had a higher rate of correctly entered data fields (94.5% versus 90.8%, p =.004) and significantly more error-free records (p = .003). The most common types of errors were failure to enter data on a required field, misspelling character variables, incorrect format for dates, and adding unit labels to strictly numeric fields. The estimated overall error rate if field restrictions had been applied was 2.3%.

CONCLUSIONS: Feasibility outcomes integral to completion of an internet-based, multi-site study were successfully achieved. Further development of programmable electronic safeguards is indicated. The error analysis conducted in this study will aid design of specific field restrictions for electronic CRFs, an important component of clinical trial management systems.

INTRODUCTION OF A GLOBAL PRIMARY CARE GRID: ADOPTION AND DISSEMINATION OF THE ePCRN ARCHITECTURE (ePCRN 8)

Peterson K, Delaney B, Arvanitis T, Sims I, Speedie S, Taweel A, Pace W, Janowiec M

BACKGROUND: Throughout the world primary care providers are increasingly adopting electronic health records (EHRs). In 2007, use of EHRs was determined by the American Academy of Family Physicians to include 40% of its membership. In the United Kingdom virtually all primary care clinics are connected to the National Health Service backbone. Although primary care practices are often distributed geographically, emerging Grid technologies are capable of providing seamless and scalable access to wide-area distributed data resources and presenting them as a single, unified resource. The

emergence of standardized data models in primary care and the widespread acceptance of improved classification systems have made it possible to create a secure, flexible, and highly automated Primary Care Grid enabled platform linking primary care clinical data sets from across the world.

METHODS: The Primary Care Grid is comprised of implementations and extensions of the Globus OGSA-DAI framework first implemented by the electronic Primary Care Research Network (ePCRN). Globus servers are introduced at primary care practices with the ability to import standardized XML strings provided by local data sources such as EHRs, pharmaceutical data, or legacy data converted into a standardized XML string. The Globus client is introduced at a research "portal" with secure connections to servers provided by PKI encryption. The data appears as a 'virtual' single dataset to the client, and can be exploited in multiple ways depending on the data contents.

RESULTS: The Primary Care Grid provides a single secure infrastructure for developing peer-to-peer sharing of medical datasets involving a worldwide consortium of primary care clinicians. The following implementations demonstrate both the flexibility and wide dissemination of ePCRN-based Globus technology in construction of a Primary Care Grid.

1. The Distributed Ambulatory Research in Therapeutics Network (DARTNet) is a federated network of electronic health record (EHR) data involving eight organizations representing over 200 clinicians and over 350,000 patients. Built upon the ePCRN architecture, DartNet captures, codifies and standardizes over 200 unique EHR data elements per patient for up to 24 months to address questions concerning the safety and effectiveness of medications and medical devices. (University of Colorado, Prime-AHRQ)
2. The National PBRN Resource Center funded by the Agency for Health Research and Quality will be supporting dissemination of the ePCRN software among registered PBRNs. (University of MN, Westat Inc, Prime-AHRQ)
3. The National Institute for Health Research, England is supporting the initial replication of an ePCRN research portal and standardized "Gateway" technologies for National Health Service primary care practices. A full implementation of ePCRN-UK was recently submitted to the Welcome Trust, UK.
4. The European Union (Framework VII) reviewed a submission for implementation of the ePCRN in the European Union, although the initial score did not allow funding.
5. Presented at the World Association of Primary Care Physicians (WONCA) in Singapore in 2007, requests for replication of the ePCRN have been received from Australia, China, and South Africa.
6. The Coordinating Center for Health Information and Service at the Centers for Disease Control and Prevention and the Federal Drug Administration are evaluating the use of Globus networks for primary care data collection.

CONCLUSION: Widespread acceptance of the PCROM as an appropriate ontology for primary care research, requests from diverse locations, and funding of new ePCRN implementations provide evidence for widespread adoption and dissemination of ePCRN technology in primary care settings.

ePRISM: AN ELECTRONIC VERSION OF THE PROJECT TO REVIEW AND IMPROVE STUDY MATERIALS (PRISM) (ePCRN 9)

Peterson K, Mendenhall T, Schendel M, Raghunath L

BACKGROUND: In 2006, Group Health Center for Health Studies published a Readability Toolkit[1] to help research teams develop study materials that participants can easily read and understand. Most informed consent documents are written at a 10th grade reading level, however, nearly half of American adults read at or below an 8th grade reading level. To support multi-site IRB applications and assure the readability of the electronic Primary Care Research Network (ePCRN) consent forms, ePCRN identified the need to enhance this toolkit by building an electronic version.

DESIGN: The PRISM Toolkit's Writing Checklist provides the basis for the components of ePRISM. Standard language is available for insert and an edit functions allow the user to insert new and study specific content. Help menus assist with replacement of overly complex words. At the completion of each section the Flesch-Kincaid Grade Level is provided. Standard consent form sections are incorporated: introduction, study purpose, study procedures, risk of study participation, benefits of study participation, alternatives to study participation, study costs and compensation, Research related injury, confidentiality, personal health information, voluntary nature of study, contacts and questions, and statement of consent. ePRISM is written in Visual Basic.NET (VB.NET), an object-oriented computer language with the use of a PostGres database. At the completion of the content, a Word version of the consent form is generated.

RESULTS: The ePRISM toolkit provides the researcher with the ability to provide consent forms at a known readability score. Existing consent language can be publicly or privately stored and revised. Additional tools are provided to improve readability including prompts for plain language, active voice and formatting.

CONCLUSIONS: ePRISM provides researchers with an initial tool to help in standardizing human subjects applications. ePRISM provides an accessible means to produce informed consent material at a targeted reading level with an easy to use template and an export to Word document. Future development of additional standardized patient communication tools is possible with this tool.

[1] Ridpath, Jessica; Center for Health Studies Readability Toolkit. 2nd ed. Seattle: Group Health Center for Health Studies; 2006.

eCRF DESIGNER: INTUITIVE DYNAMIC SEMANTICALLY INTEROPERABLE CASE REPORT FORMS DESIGNER WITH ISO-11179 AND CADSR COMPATIBILITY (ePCRN 11)

Delaney B, Taweel A, Zhao, L, Peterson K, Arvanitis T, Speedie S, Janowiec M., Sim I, Hobbs R

BACKGROUND: One of the most challenging tasks for running a randomized controlled trial (RCT) is to design data aware and action enabled case reports forms (CRF) to follow up and collect participants' data. Traditionally CRFs are paper-based although recently more electronic-based CRF (eCRF) are being used in clinical trials. Currently, simple eCRFs are either created using specific templates, e.g. Excel-based, or formats. However, more complex eCRFs, that can validate data entered and store meta-data annotations,

require intelligent programming support, and usually created by a professional programmer. Various clinical trial management systems started adding tools to create CRFs but with limited capabilities. The caBIG Form Builder was amongst the first CRF designers to enable the creation of CRF-structures using common data elements (CDE) concepts. Using CDEs enables the creation of CRF-structures that are more semantically interoperable and re-usable across studies. However these CRF-structures provide only structural contents and lack data awareness, dynamic action and validation awareness and graphical features and capabilities. The ePCRN eCRF Designer has been created to overcome these limitations. The eCRF Designer enables creation of CRFs from ISO-11179 compatible CDEs as its basic elements, which can be newly created or imported from an ISO-11179 store. These CRFs can be enriched by meta-data and graphical attributes. The created forms are then automatically generated and dynamically deployed within the ePCRN clinical management system. These forms can be exported for re-use or imported directly from the caBIG caDSR repository.

OBJECTIVE: To develop a tool, as part of an overall clinical trial management system (CTMS), to design semantically interoperable, data aware and dynamic and ISO-11179 compatible case report forms that can be easily created and dynamically deployed for use to allow collecting participant trial data.

METHOD: A dynamic graphical interface was designed, based on a prior requirements analysis. It enables creating ISO-11179 compatible data elements and data and action aware case report forms. It allows automatic generation of and dynamic deployment of these CRFs for use. It also allows importing and exporting semantically interoperable CRF forms from the caDSR or any other compatible CDE repository.

RESULTS: The eCRF designer can be used to create or import already created eCRFs. Created or imported eCRFs can be enriched with meta-data and graphical capabilities and can be exported for re-use or dynamically deployed into clinical trial management systems. Deployed forms are used to collect participant information and enable following up a participant electronically across multiple centers.

CONCLUSIONS: The ePCRN eCRF designer tool has the potential to greatly facilitate creating clinical trials case report forms and increase their availability and re-use across multiple studies. This decreases the complexity, cost and effort of creating CRFs, and promotes reuse of data elements and templates within clinical trials units, across centers and across clinical domains.

PRIMARY CARE RESEARCH STORYBOARD: USE CASES AND ACTIVITY DIAGRAMS FOR A PRACTICE-BASED RANDOMIZED CLINICAL TRIAL (ePCRN 12)

Delaney B, Taweel A, Peterson K, Arvanitis T, Speedie S, Janowiec M., Sim I, Hobbs R

BACKGROUND: One of the essential tasks in capturing clinical trials elements, such as protocol, eligibility criteria etc, is also to understand the trial protocol enactment process. However, a trial protocol enactment process is different from one trial to another. This introduces a major obstacle to designing a clinical trial design system or clinical trial management system. In ePCRN, to overcome this obstacle, a generic randomized clinical trial design and enactment process was captured using UML as a business process using activity diagrams. The outcome was a critical step to enable a better understanding of designing and enacting trials in primary care. Although the focus was on practice based

primary care research, these processes can be used for other clinical domains. The resultant activity diagrams played a critical role in designing the ePCRN infrastructure, clinical researcher workbench and its user graphical interface.

OBJECTIVE: To capture and model clinical trial design and enactment processes, that were used as a basis to design ePCRN trial protocol and eligibility criteria design workbench and tools.

METHOD: The clinical trial protocol design and enactment business processes was modeled using UML modeling method and activity diagrams. The modeling involved an extensive session between computer scientists, UML modeling experts, domain users and domain clinical trials. Each of the business processes were discussed extensively and revised by specialist teams. The modeling process involved defining standards terminology to enable semantic interoperability and facilitate their reuse by other clinical domains. To enable compatibility with other efforts, the modeling process also involved comparing and contrasting with BRIDG.

RESULTS: The final activity diagrams represent a reference business process that can be used as a reference for clinical trial design and enactment process in primary care. These diagrams captured the control flow of the clinical trials enactment activities using standardized terminology and incorporating different conditional flows. There are four top-level main activities, namely, Plan Study, Set Up Study, Execute Study and Analyze study.. Each of these activities includes numerous sub-activities. The resultant enactment processes were then used to inform the software development and design of the ePCRN workbench and tools.

CONCLUSIONS: The design and enactment process is modeled and captured as business and control flow processes and activities for a generic practice based randomized clinical trial in a primary care setting. The model can be used to model clinical trials process and clinical trials management systems in other clinical domains.

DEMONSTRATION OF THE ePCRN ARCHITECTURE FOR PRIMARY CARE RESEARCH

Peterson K[1], Delaney B[2], Speedie S[1], Sim I[3], Taweel A[2], Janowiec M[1], Lange C[1]

[1]University of Minnesota, Minneapolis, MN; [2]University of Birmingham, England; [3]University of California, San Francisco

DESCRIPTION: This will be a five minute demonstration the ePCRN software. ePCRN will demonstrate the ability to perform live searches of clinical datasets for medical problems, laboratory values, medications and specific patient characteristics. The demonstration will show how the researcher interacts with Network Directors for opportunistic identification of eligible subjects, identification of standardized concepts and retrieval of appropriate codes. Clinical information about the study will be reviewed by the patient's provider and, if appropriate, forwarded to the patient. Finally, with appropriated consent, a subject's information is moved in to the Clinical Trials Management System.

COG – Gregory Reaman, MD

SUCCESSFUL TEST OF INTEROPERABILITY OF THE ESTABLISHED CHILDREN'S ONCOLOGY GROUP CLINICAL TRIAL INFRASTRUCTURE: RESULTS OF THE COG-PBMTC COLLABORATION

Donna Wall, MD[1], Dolly Yang, MPH[2], Kirk Schultz, MD[3], Anita Khayat, PhD[2], Joe Woelkers, MA[2], John Levine, MD[4], Alan Gamis, MD[5], Gregory Reaman, MD[2]

[1]Texas Transplant Institute, Pediatric Blood and Marrow Transplantation, San Antonio, TX, United States; [2]Children's Oncology Group, COG Operations Office, Arcadia, CA, United States; [3]University of British Columbia, Pediatric Hematology/Oncology, Vancouver, Canada; [4]University of Michigan, Pediatric Blood and Marrow Transplantation, Ann Arbor, MI, United States; [5]Kansas City Mercy Hospital, Pediatric Hematology/Oncology/ Transplant, Kansas City, MO, United States

PURPOSE: The increasing complexity of clinical trial informatics, monitoring, and oversight requires major commitment to research infrastructure. In response to an NIH-initiated broad agency appeal (BAA-RM-04-23 Re-Engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks), the Children's Oncology Group (COG) and the Pediatric Blood and Marrow Transplant Consortium (PBMTC) embarked on an endeavor to utilize and expand the existing clinical trial operations of COG to support the transplant specific trials of the PBMTC.

METHOD: The COG administration and transplant discipline worked closely with the PBMTC in the development of 3 transplant trials. In the process, standardized informatics tools that allow for optimal data sharing of clinical research data from clinical trials between the COG/PBMTC and other networks were developed. A clinical trial administrative infrastructure was developed within the PBMTC to mesh with COG operations. COG informatics support for education modules, data capture, and study monitoring was enhanced for transplant trial needs.

RESULTS: All 3 trials have opened to accrual. ASCT0521/SUP051 opened in 2006, and 42 centers are involved in this phase II trial evaluating etanercept in the treatment of post-transplant idiopathic pneumonitis. ASCT0431/ONC051 opened in 2007 and to date 32 transplant centers are involved in this phase III trial evaluating m-TOR inhibition by sirolimus as both an immunosuppressive and antileukemic agent following allogeneic transplant for ALL. ASCT0631/SCT051 has just opened and will test whether GCSF stimulation of donors improves outcome in children undergoing allogeneic BMT. In addition, this initiative has allowed for a collaborative performance of a phase III trial, BMT CTN 0501, testing one versus two cord blood units as a stem cell source between the COG, PBMTC, and BMT CTN and the development of a future Thalassemia phase II trial.

CONCLUSION: This collaborative effort demonstrates the ability to expand a clinical trial network infrastructure to support a broader range of trial activity.

RIOS NET – Robert Williams, MD

EXPANSION AND INTEROPERABILITY OF CLINICAL RESEARCH NETWORKS IN UNDERSERVED, UNDERREPRESENTED POPULATIONS

Robert L. Williams, MD,MPH; Wilson Pace, MD; Elvan Daniels, MD; Bennett Parnes, MD; Robert Volk, PhD; Michael Potter, MD; Margaret Handley, PhD; Robert Rhyne, MD; Robert Leverence, MD; Philip Kroth, MD,MS

BACKGROUND: Minority communities have traditionally been relatively underrepresented in clinical research, and likewise, clinical research has not always focused on the needs and circumstances of minority communities. Historical experience with research has reduced trust in researchers by many minority communities. Expansion and increased interoperability of clinical research networks that focus on research in minority communities must incorporate certain principles to be successful, including: partnership, mutual benefit, cultural grounding, adaptation to local circumstances, targeting priority health topics. Likewise, integration of community clinicians working in underserved communities must be based on these same principles.

METHODS: RIOS Net (Research Involving Outpatient Settings Network), a primary care practice-based research network composed of clinicians practicing in medically underserved Hispanic and Native American communities, expanded its membership, its community involvement, and its scope of research. Interoperable collaborations were established with other practice-based research networks sharing a similar interest in the health and health care of underserved communities. Expansion and linkage with other networks was based on the guiding principles listed.

RESULTS: RIOS Net membership approximately doubled to 275 and community participation increased (as measured by numbers of communities involved and requests for participation) through: dedicated staff supporting outreach, communication and education; shared planning and decision-making; focus on member and community member health topic priorities; bidirectional benefits. The PRIME Net (Primary Care MultiEthnic Network) consortium was developed and expanded beyond the original planned set of three networks as a result of: formalizing collaborative planning and decision-making; flexible and robust IS infrastructure and support that accommodates to differences in network structures; focus on research of interest to networks and their members and community members; centralized leadership of regulatory processes; resource sharing. Stepwise research development in the consortium tested collaborative planning, decision-making, IS support, data collection, analysis, and reporting. Study topics included management of hepatitis C, management of chronic non-malignant pain, and a six-stage multi-method study of acanthosis nigricans and clinician behavior.

CONCLUSIONS: When based on key principles of collaborative research, clinical research networks in traditionally underrepresented communities can support expansion of research and interoperable consortia with similarly interested networks. The history of research in such communities and the nature of collaboration with community clinicians mandates ongoing infrastructure and processes devoted to communication and mutual benefit of the research endeavor, with associated costs.

IECRN WESTAT – Stephen Durako

BARRIERS TO AND FACILITATORS OF EFFECTIVE NETWORK FUNCTIONING: RESULTS OF THE INVENTORY AND EVALUATION OF CLINICAL RESEARCH NETWORKS (IECRN) PROJECT

Steve Durako, Paula Darby Lipman, and Nancy Dianis
Westat, Rockville, MD

A goal of the Inventory and Evaluation of Clinical Research Networks (IECRN) project, which seeks to enhance the efficiency and productivity of clinical research, was to prepare a detailed description of existing clinical research network (CRN) practices from a sample of identified CRNs. Descriptive Surveys were conducted with members of a sub sample of CRNs to gather detailed information about network practices. Interviews were conducted with respondents to identify and explore the barriers and facilitators associated with these practices. A National Leadership Forum was held to bring together the clinical research community to discuss project findings and the feasibility of adapting practices identified as most effective into their own research environments.

Valuable insights on barriers, facilitators, and “lessons learned” associated with adoption and implementation of network practices were gained through both the survey data collection and the input from Forum participants. Qualitative findings will be presented regarding how to overcome barriers associated with management, governance, and regulatory issues; data management and information technology, staff training and professional development, and recruitment and retention.

The presentation of these data seeks to foster collaboration, facilitate information and practice sharing among networks, and to stimulate the discussion of possible best practices for clinical research networks. The IECRN is funded by the National Institutes of Health (NIH) and led by the National Center for Research Resources (NCRR). It stems from the NIH’s commitment to re-engineer the clinical research enterprise, one of the key objectives of the NIH Roadmap for Medical Research.

MANAGEMENT, GOVERNANCE AND FINANCIAL PRACTICES OF RESEARCH NETWORKS: RESULTS OF THE INVENTORY AND EVALUATION OF CLINICAL RESEARCH NETWORKS (IECRN) PROJECT

Paula Darby Lipman, Nancy Dianis, and Steve Durako
Westat, Rockville, MD

A goal of the Inventory and Evaluation of Clinical Research Networks (IECRN) project, which seeks to enhance the efficiency and productivity of clinical research, was to prepare a detailed description of existing clinical research network (CRN) practices from a sample of identified CRNs. Descriptive Surveys were conducted with members of a sub sample of CRNs to gather detailed information about the practices that each CRN employs to organize and conduct research.

Key findings from two of the survey modules will be presented. The Management and Governance instrument addressed the research focus of the network, staff composition; policies, procedures, and practices related to creation and dissemination of findings; and policies and practices relating to scientific productivity. The instrument also assessed presence and content of bylaws and standard operating procedures; organizational roles

and functions; decision-making processes; establishing the scientific agenda; leadership; policymaking and evaluation. The Financial Practices instrument asked about funding issues, policies and practices; current sources and types of network funding; fundraising efforts; cost structure and coverage, cost accounting and accountability; and challenges of and responses to managing funds to accomplish the network's goals and objectives.

The presentation of these data seeks to foster collaboration, facilitate information and practice sharing among networks, and to stimulate the discussion of possible best practices for clinical research networks. The IECRN is funded by the National Institutes of Health (NIH) and led by the National Center for Research Resources. It stems from the NIH's commitment to re-engineer the clinical research enterprise, one of the key objectives of the NIH Roadmap for Medical Research.

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Lee Green, MD
Dennis Confer, MD

NIH Roadmap Programs - 2008
List of Investigator Publications

INVESTIGATOR GROUP

PUBLICATION IN PRESS:

Williams RL, Johnson SB, Greene SM, Larson EB, Green LA, Morris A, Confer D, Reamon G, Madigan R, Kahn J. Signposts along the National Institutes of Health's Roadmap for Re-engineering Clinical Research: Lessons from the Clinical Research Networks Initiative. Arch Int Med 2008

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LEE GREEN, MD

University of Michigan, Ann Arbor, MI

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DENNIS CONFER, MD

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CAROL DUKES-HAMILTON, MD

Duke University, Durham, NC

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Carol Dukes Hamilton, MD, and Kimberly Booher, IDSA, Abstract and Poster Presentation; Toronto, Ontario, Canada, October 12-14, 2006

Ann Mosher, RN, Carol Dukes Hamilton MD, PRIM-R Conference, 2 Abstracts; 2 Poster Sessions; Oral Presentation, Washington, DC, November 15-16, 2006

Carol Dukes Hamilton, MD, National Conference on Alternative IRB Models: Optimizing Human Subject Protection; Abstract, Poster, and Oral Presentation; Washington, DC, November 19-21 2006

Bron Kisler and Carol Dukes Hamilton, MD, Drug Information Association Conference, Abstract and Oral Presentation, Atlanta, GA, June 18-21, 2007

Carol Dukes Hamilton, MD, and Kimberly Booher, IUATLD Meeting, Abstract and Poster Session; Capetown, South Africa, November 8-12, 2007

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Carol Dukes-Hamilton, MD

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Anita Walden, caBIG Boot Camp Training Conference, Oral Presentation, Rockville, MD, August 4, 2006

Anita Walden, Archetype Meeting, Oral Presentation, Boca Raton, FL, September 8-10, 2006

Anita Walden, HL7 Meeting, Oral Presentation, Boca Raton, FL, September 10-15, 2006

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ROBERT HARRINGTON, MD

Duke University, Durham, NC

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STEPHEN JOHNSON, PHD

Columbia University, New York, NY

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JAMES KAHN, MD

University of California SF, San Francisco, CA

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Representing complex regimen data in the CNICS (CFAR Network of Integrated Clinical Systems) cohort. SDW Frost 1, C Mathews1, M Saag2, M Kitahata3, B Rodriguez4, J Kahn5, S Boswell6, B Lober3, M Lederman4, S Sun1, AFY Poon1, S Jain1, RH Haubrich1, and the CNICS Study Team XVI International HIV Drug Resistance Workshop June 12-15, 2007 Bridgetown, Barbados, abstract 153

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J. RICHARD LANDIS, PHD

University of Pennsylvania, Philadelphia, PA

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Penn Center for Clinical Trials, Overview of Structure and Functions to the University of Pennsylvania School of Medicine Clinical Research Enterprise, Chairs and Senior Faculty Meeting; Fromell, G., July 2005

Information Technology and Clinical Research: A Practical Application of Information Technology to Research Infrastructure to the American Association of Medical Colleges, Group on Information Resources; Fromell, G., April 2005

Oracle SiteMinder Project Overview to the Office of Human Research Faculty Advisory Committee; Fromell, G., April 2005

Vision for IT Support of Clinical Research: A Case Study to the Association of American Health Centers, Clinical Research Forum: "Bring Your CIO"; Fromell, G., March 2005

Enhancing Infrastructure for Clinical Research: A Model Focused on the Research Team to the Penn Medicine IT Committee; Fromell, G., February 2005

ERIC LARSON, MD, MPH

Group Health Cooperative Seattle, WA

Presentations and Posters:

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ALAN MORRIS, MD

LDS Hospital, Salt Lake City, UT

Abstracts and Presentations

K.A. Sward, MS,RN, A.H. Morris, MD, D. Sorenson, PhD, L. Weaver, MD, C. Grissom, MD, H.R. Warner, MD,PhD and for Reengineering Clinical Research in Critical Care Network. A Software Tool to Develop Computerized Bedside Clinical Protocols. [Abstract]. AJRCCM. 2007; 175: A793

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KEVIN PETERSON, MD, MPH

University of Minnesota, Minneapolis, MN

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Kevin Peterson, MD, MPH

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GREGORY REAMAN, MD

National Childhood Cancer Foundation, Arcadia, CA

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ROBERT L. WILLIAMS, MD, MPH

University of New Mexico, Albuquerque, NM

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Stephen Durako

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STEPHEN DURAKO

Westat, Rockville, MD

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Contact	Program/Affiliation	Email
Dr. Jeffrey S. Abrams	NIH	abramsj@mail.nih.gov
Krishika Acharya	NIH	acharyak2@mail.nih.gov
Dr. Beena Akolkar	NIH	akolkarb@mail.nih.gov
Akgul Akpinarli	NIAID/NIH	aakpinarli@niaid.nih.gov
Dr. Deborah I. Allen	ePCRN	diallen@iupui.edu
Dr. Krishan K. Arora	NIH	arorak@mail.nih.gov
Dr. Brian D. Athey	University of Michigan-Palmer Commons	bleu@umich.edu
Dr. Prabha L. Atreya	NIBIB/Office of Scientific Review /NIH	atreyapr@mail.nih.gov
Gale Auguste	NIH	ga85u@nih.gov
Elaine Ayres	NIH	eayres@cc.nih.gov
Seong-Yi Baik	University of Cincinnati	seongyi.baik@uc.edu
Dr. Suzanne Bakken	COLUMBIA	sbh22@columbia.edu
Dr. M. Edwina Barnett	RTRN Data Technology Coordinating Ctr	m.edwina.barnett@rtrn.net
Franca Benedicty Barton, MS	The EMMES Corporation	fbarton@emmes.com
Dr. Philip J. Baty	TRINITY HEALTH ORG	batyp@trinity-health.org
Jean Baum, NIMH	DSIR, NIMH	jbaum@mail.nih.gov
John Beigel, M.D.	NIH	jbeigel@niaid.nih.gov
Dr. Stefano Bellon	Padova	info@stefanobellon.it
Ken Bengtsson	AGNIS	kbengtss@nmdp.org
Adam Bennett	NIH/NCI	bennettad@mail.nih.gov
Dr. Florence Béranger	French Embassy-Inserm	inserm-usa@ambafrance-us.org
Linda B. Berman	Social & Scientific Systems, Inc	lberman@s-3.com
Dr. Stefano Bertuzzi	NIH	stefano_bertuzzi@nih.gov
Dr. Himani Bisht	NIH	hbisht@niaid.nih.gov
Dr. Carol J. Blaisdell	NIH	blaisdellcj@nhlbi.nih.gov
Meryl F. Bloomrosen	NIH	meryl@AMIA.ORG
Martin B. Blumsack	NIH	blumsack@nih.gov
Dr. Olivier Bodenreider	NIH	olivier@nlm.nih.gov
Johannes M. Boehme	Wake Forest Univ School of Medicine	jboehme@wfubmc.edu
Dr. Robert F. Bonner	NIH	bonnerr@mail.nih.gov
Kimberly Booher	TB Trials Network	kimberly.booher@duke.edu
Dr. Lynn Bosco	NIH	boscol@od.nih.gov
Christopher Bourdeau	Rockville, MD	cbourdeau@ctisinc.com
Dr. Olga Brazhnik	NIH	brazhnik@nih.gov
Dr. Erica Breslau	NCI/NIH	breslaue@mail.nih.gov
Dr. Apryl R. Brown	CRN Harmony	aprylrbrown@yahoo.com
Suanna S. Bruinooge	American Society of Clinical Oncology	bruinoos@asco.org
Philip M. Budashewitz	NCI/Office of International Affairs / NIH	budashewitzp@mail.nih.gov
Dr. Mary Rose Burnham	Foundation for Healthy Living	mrburnham@gmail.com
Barbara Butler	NIH	bdscofield@earthlink.net
John M. Campbell	Northrop Grumman IT, Health Solutions	John4.Campbell@ngc.com
Thomas E. Cannady	Hyattsville, MD	thomascannady@netscape.com
Dr. Jacek Capala	NIH	capalaj@mail.nih.gov
German Cavelier, PhD	NIH	gcavelier@mail.nih.gov
George Chacko, PhD	NIH	chackoge@csr.nih.gov

Contact	Program/Affiliation	Email
Amar Chahal MD	Fremont, CA	achahal@velos.com
Dr. Natalia Chalmers, D.D.S.	NIH	nchalmers@mail.nih.gov
Dr. Charles V. Chesson	Silver Spring, MD	mjackson@s-3.com
Huey Cheung	NIH	cheungh@mail.nih.gov
Dr. HyeRan Choo	Bethesda, MD	hyeranchoo@gmail.com
Dr. Gary G. Christoph	Columbia, MD	gary.christoph@ngc.com
Dr. Christopher G. Chute	MAYO	chute@mayo.edu
Denise Cifelli	CRN Harmony	cifelli@mail.med.upenn.edu
Dr. James J. Cimino	NIH	ciminoj@mail.nih.gov
Gina P. Clemons	VA R&D Communications	Gina.Clemons@va.gov
Dr. Zohara Cohen	NIH	zcohen@mail.nih.gov
Dr. Elaine Collier	NIH	ec5x@nih.gov
Stacy Collins	Silver Spring, MD	stacy.collins@enacct.org
Dennis Confer, M.D.	National Marrow Donor Program	dconfer@nmdp.org, thousema@nmdp.org
Barbara Conley, MD	East Lansing, MI	barbara.conley@hc.msu.edu
Dr. Lawton S. Cooper	NIH	cooperls@nhlbi.nih.gov
Milton Corn, M.D.	NIH	cornm@mail.nih.gov
Dennis J. Cotter	Bethesda, MD	dcott@mtppi.org
Joseph Croghan	Reston, VA	jcroghan@5amsolutions.com
Carol A. Cushing, R.N.	NIDA/NIH	ccushing@nida.nih.gov
Carl Dahlke	CTN Best Practices	Carl.Dahlke@ngc.com
Dr. Mary Jo Deering	NCI Center for Biomedical Informatics	deeringm@mail.nih.gov
Dr. Brendan C. Delaney	ePCRN	b.c.delaney@bham.ac.uk
Yvette Delph	Silver Spring, MD	mjackson@s-3.com
Dr. Robert A. Dennis	UCLA	buddy@ucla.edu
Dr. Donald J. DeNucci	NIH	denuccid@nidcr.nih.gov
Dr. Louis V. DePaolo	NIH	ld38p@nih.gov
Dr. Marta L. De Santis	NIH	mdesantis@nida.nih.gov
Dr. Michael P. Diamond	WAYNE STATE	mdiamond@med.wayne.edu
Nancy L. Dianis, RN, MS	Westat	nancydianis@westat.com
Deborah Dietz	Silver Spring, MD	mjackson@s-3.com
Nancy DiFronzo, Ph.D.	DBDR, NHLBI, NIH	difronzon@nhlbi.nih.gov
William DiGrazio	Rochester, NY	will_digrazio@urmc.rochester.edu
Dr. Robert P. DiLaura	Cleveland, OH	dilaurr@ccf.org
Dr. Raymond A. Dionne	NIH	dionner@mail.nih.gov
Donna Dlubac	Silver Spring, MD	DDlubac@s-3.com
Rowena Dolor, MD	Duke Primary Care Research Consortium	rowena.dolor@duke.edu
Arban Domi	NIH	adomi@niaid.nih.gov
Dr. Demetrio Domingo	NIH	ddomingo@mail.nih.gov
Dr. Leah Rae Donahue	The Jackson Laboratory	LeahRae.Donahue@jax.org
Dr. Patricia D'Souza	NIH	pdsouza@niaid.nih,gov
Carol Dukes Hamilton	TB Trials Network	dukes002@mc.duke.edu
Patrick Dunn, Ph.D.	NIH	patrick.dunn@ngc.com
Dr. Sarah E. Dunsmore	NIH	dunsmores@nigms.nih.gov
Steve Durborow	CRN Harmony	sdurboro@upenn.edu
Debra A. Egan	NIH	debrae@nhlbi.nih.gov

Contact	Program/Affiliation	Email
Dr. David Eichmann	University of Iowa	david-eichmann@uiowa.edu
Dr. Esther Eisenberg	NIH	eisenbes@mail.nih.gov
Dr. Cerise L. Elliott	NIH	elliottce@mail.nih.gov
Shellie D. Ellis	Translational Science Institute	sheellis@wfubmc.edu
Kolaleh Eskandanian, PhD, MBA	GEORGETOWN	eskandk@georgetown.edu
Dr. Christina R. Esperat	Texas Tech University Health Sciences Cn	christina.esperat@ttuhsc.edu
Bernard G. Ewigman, MD, MSPH	Univ. of Chicago - Dept. of Family Med.	bewigman@uchicago.edu
Wendy Fanaroff	NIH	wf44q@nih.gov
Dr. Yang Fann	NIH	fann@ninds.nih.gov
Dr. Greg Farber	NIH	farberg@mail.nih.gov
Dr. Rosemarie Filart	NIH	filartr@mail.nih.gov
Dr. Lawrence J. Fine	NIH	finel@mail.nih.gov
Dr. Richard Fisher	NIH	nano@nih.gov
Claire Flaherty-Craig, PhD	Penn State College of Medicine	ccraig@hmc.psu.edu
Dr. Valerie Florance	NIH	vflorance@earthlink.net
Dr. Paul Fontelo	NIH	fontelo@nlm.nih.gov
Dr. Gabriel B. Fosu	NIH	fosug@csr.nih.gov
Brent Gendleman	Phoenix, AZ	bgendleman@5amsolutions.com
Dr. Jenenne A. Geske	NIH	jgeske@unmc.edu
Dr. Misrak Gezmu	NIH	mgezmu@niaid.nih.gov
Amrita Ghosh	NIH	aghosh1@mail.nih.gov
Dr. John R. Glowa	NIH	glowaj@mail.nih.gov
Dr. Elizabeth W. Gonzalez	Drexel University	ewg22@drexel.edu
Dr. Rashmi Gopal-Srivastava	NIH	gopalr@mail.nih.gov
Dr. Sharon M. Gordon	NIH	sgordon@umaryland.edu
Dr. Paul Grant	NIH	paul.grant@mail.nih.gov
Lee Green, MD MPH	MCRC	greenla@umich.edu
Sarah M. Greene	HMORN CCSN	greene.sm@ghc.org
Sharon Greenwell	NIH	sg115f@nih.gov
Dr. Tom P. Gross	FDA	thomas.gross@fda.hhs.gov
Dr. Zhiping Gu	NIH	zhiping.gu@ngc.com
Dr. Yongjian Guo	NIH	guoyo@mail.nih.gov
Kailash Gupta, PhD	NIAID/NIH	kgupta@niaid.nih.gov
Dr. Ranjan Gupta	Office of Global Research, NIAID/NIH	guptar@mail.nih.gov
Dr. Adam Haim	NIH	haima@mail.nih.gov
Dr. Xuemeng Han Sarro	NIH	xsarro@niaid.nih.gov
Paul Harris, PhD	Nashville, TN	paul.harris@vanderbilt.edu
Ahmed Hasan, MD	NIH	hasana@ nhlbi.nih.gov
Kathryn Hassell, MD	NIH	hassellk@nhlbi.nih.gov
Dr. David Hau	NIH	haudt@mail.nih.gov
Dr. Anthony R. Hayward	NIH	haywarda@mail.nih.gov
Christopher P. Helker	CRN Harmony	chelker2@mail.med.upenn.edu
Betsey R. Herpin	NIH	herpinb@niaid.nih.gov
Tony Hess, PhD	Rockville, MD	ahess@ctisinc.com
Sharon E. Hesterlee, Ph.D.	Tucson, AZ	shesterlee@mdausa.org
John Hickner, MD, MSc	Chicago, IL	jhickner@uchicago.edu

Contact	Program/Affiliation	Email
Dr. Jennifer A. Hobin	Bethesda, MD	jhobin@faseb.org
Dr. Karen J. Hofman	Fogarty International Center, NIH	hofmank@mail.nih.gov
David Holland	TB Trials Network	hendr025@mc.duke.edu
Maria Hondras	Davenport, IA	maria.hondras@palmer.edu
Dale A. Hunscher	MCRC	dalehuns@umich.edu
Dr. Yentram Huyen	NIH	huyeny@niaid.nih.gov
Dr. Norman T. Ilowite	Children's Hospital at Montefiore	nilowite@montefiore.org
Mark Janowiec	ePCRN	janow005@umn.edu
Dr. LeeAnn Jensen	NIH	jensenl@nih.gov
Dr. George Jiang		jiang_george@bah.com
Dr. Stephen B. Johnson	Intertrial	sbj2@columbia.edu
Dr. Laura L. Johnson	NIH	johnslau@mail.nih.gov
Dr. Calvin A. Johnson	NIH	johnson@mail.nih.gov
Loretta Jones	Los Angeles, CA	LJonesHAAF@aol.com
Douglas J. Joubert	NIH	joubertd@ors.od.nih.gov
Dr. Jonathan M. Kagan	NIAID/NIH	jkagan@niaid.nih.gov
Dr. James Kahn	CNICS	jkahn@php.ucsf.edu
Stephen G. Kaler MD	NIH	kalers@mail.nih.gov
Michael J. Kamerick	UCSF	michael.kamerick@ucsf.edu
Dr. Peter G. Kaufmann	NIH	kaufmannp@nhlbi.nih.gov
James Kaylor	CRN Harmony	jkaylor@mail.med.upenn.edu
Margaret Keil	NIH	keilm@mail.nih.gov
Grace Kelly	NIAID/NIH	gkelly@niaid.nih.gov
Dr. Kathleen A. Kelly	Newtonville, NY	KKelly05@nycap.rr.com
Annie Kennedy	Washington, DC	akennedy@mdausa.org
Rachel F. Kidwiler	GEORGETOWN	rfk7@georgetown.edu
Dongkyu Kim	Georgetown	dkkim@isis.georgetown.edu
Ruth Kirby	NIH	kirbyr@nhlbi.nih.gov
Dr. Barbara B. Knowles	The Jackson Laboratory	barbara.knowles@jax.org
Patricia C. Kobor	American Psychological Association	pkobor@apa.org
Dr. Sarah Kobrin	NIH	kobrins@mail.nih.gov
Terrie L. Kolodziej	NIH	kolodziejt@niaid.nih.gov
Dr. Neil J. Korman	Dept Dermatology University Hospitals	njk2@case.edu
Amy Krafft, PhD	RDB/DMID/NIAID/NIH	kraffta@niaid.nih.gov
Dr. Selma C. Kunitz		skunitz@kai-rsearch.com
Brenda Kunkel	Bethesda, MD	bkunkel@us.ibm.com
Dr. John W. Kusek	NIH/NIDDK	KusekJ@mail.nih.gov
Dr. Igor A. Kuzmin	NIH	kuzmini@mail.nih.gov
Lauren E. Laimon	Westat	laurenlaimon@westat.com
J. Richard Landis, Ph.D.	CRN Harmony	jrlandis@mail.med.upenn.edu
Carol J. Lange	ePCRN	lange076@umn.edu
Dr. Eric B. Larson	HMORN CCSN	larson.e@ghc.org
Dr. Maxwell P. Lee	NIH	leemax@mail.nih.gov
Dr. Simon Craddock Lee	NIH	leesi@mail.nih.gov
Adam Lee	University of Maryland	adamlee@umd.edu
Dr. Juan J. Lertora	NIH	lertoraj@mail.cc.nih.gov
Gayle E. Lester	NIH	lester1@mail.nih.gov

Contact	Program/Affiliation	Email
Naomi Levinthal	American Academy of Dermatology	nlevinthal@aad.org
Roger J. Lewis, MD, PhD	Harbor-UCLA Medical Cente	roger@emedharbor.edu
Dr. Francisco J. Leyva	NIH	leyvaf@mail.nih.gov
Dr. Ingrid Y. Li	NIH	ili1@mail.nih.gov
Paula D. Lipman	Westat	PaulaLipman@westat.com
Dr. A. Roger Little	NIH	arnoldadul@mail.nih.gov
Dr. Wlodek Lopaczynski	NIH	lopacw@mail.nih.gov
John Lumpkin	NIAID/NIH	lumpkinj@niaid.nih.gov
Dr. Robert Macura		robert.macura@gmail.com
Rosemary Madigan, MS, MPH	CRN Harmony	rmadigan@mail.med.upenn.edu
Kenneth C. Malley	Fredericksburg, VA	kmalley1@verizon.net
Dr. Michael Marron	NIH	marron@nih.gov
Dr. Joanne B. Martin	Indiana University School of Nursing	jbmartin@iupui.edu
Dr. Sherry Marts	WOMEN'S HEALTH RESEARCH	sherry@womenshealthresearch.org
Dr. Padma Maruvada	NCRR, NIH	maruvadp@mail.nih.gov
Katie McCarthy	NIH	kmccarthy@bio.org
Donna Jo McCloskey, PhD, RN	NIH	mccloskd@mail.nih.gov
Dr. Jessyna M. McDonald	University of the District of Columbia	jmcdonald@udc.edu
Martha P. McMurry	OCTRI-Mail Code CR 107	mcmurrym@ohsu.edu
Patrick McShane	Woodbridge, VA	pmcshane@BJHCHS.com
Imelda Medina, M.D.	NIH	medinai@childpsych.columbia.edu
Carol Merchant, M.D.	NIH	emerchant@nih.gov
David Meyers, MD	AHRQ	david.meyers@ahrq.hhs.gov
Margo Michaels, MPH	Silver Spring, MD	info@enacct.org
Dr. Mary Ellen Michel	Clinical Trials Network, NIDA	mm108w@nih.gov
Dr. Nancy E. Miller	NIH	nm68k@nih.gov
Scott Mincemoyer RN, BS	NIH	rxm164@psu.edu
Norma Minkoff	Gaithersburg, MD	normaminkoff@yahoo.com
Paolo G. Miotti, OAR, NIH	NCI, NIH	pm122m@nih.gov
Prasun J. Mishra	NIH	mishrapj@mail.nih.gov
Phyllis Mitchell, M. S.	NIH	mitchelp@nhlbi.nih.gov
Daniel Molina		dmolina@tech-res.com
Gregory R. Moore	Rockville, MD	gmoore@ctisinc.com
Loretha Moore, Ph.D.	Fox Chase Cancer Center	Loretha.Moore@fccc.edu
Alan H. Morris, MD	Murray, UT	Elizabeth.Baraboz@imail.org
Dr. Carmen P. Moten	NIH	cmoten@mail.nih.gov
Dr. Anne Victoria Neale	Department of Family Medicine	vneale@med.wayne.edu
Dr. Lawrence M. Nelson	NIH	Lawrence_Nelson@nih.gov
Andrew F. Nelson	NIH	andrew.f.nelson@healthpartners.com
Gregory Nero	West Friendship, MD	gregory.nero@ngc.com
Dr. Robert W. Neumar	Hosp.of the University of Pennsylvania	neumarr@uphs.upenn.edu
Eileen P. Newman	NIH	eileen.newman@nih.gov
Dr. Mostafa A. Nokta	NIH	mostafa.nokta@nih.gov
Martha R. Nolan	Society for Women's Health Research	martha@womenshealthresearch.org
Dr. Leroy M. Nyberg	NIDDK.NIH	NybergL@mail.nih.gov
William R. O'Donnell	NIH	wrod@nei.nih.gov

Contact	Program/Affiliation	Email
Frederick P. Ognibene, M.D.	NIH	fognibene@cc.nih.gov
Dr. Phyllis C. Panzano	Columbus, OH	panzano.2@osu.edu
Gayle E. Paynter	Oxford, NC	gayle.e.paynter@duke.edu
Victoria Pemberton	NIH	pembertonv@nhlbi.nih.gov
Dr. Harold Perl	NIH	hperl@nida.nih.gov
Kevin A. Peterson, MD, MPH	ePCRN	peter223@umn.edu
Ray Petryshyn, Ph.D.	NIH	petryshr@mail.nih.gov
P. Kim Pham, Ph.D.	NIH	pp64n@nih.gov
Dr. Reed B. Phillips	Pocatello, ID	rphillips@fcer.org
Dr. Jerry Pierson	NIH	jerome.pierson@nih.hhs.gov
Dr. Ricardo Pietrobon	DUKE	rpietro@duke.edu
Dr. Chai C. Portera	NIH	porterac@mail.nih.gov
Dr. Arnold L. Potosky	NIH	potoskya@mail.nih.gov
Renee L. Pridgen	CTN Best Practices	renee.pridgen@duke.edu
Dr. Tony Punturieri	NIH	punturieria@nhlbi.nih.gov
Dr. Anil J. Purty	Emory University	purtyanil@sify.com
Dr. Mary Purucker	DCRR/NCRR/NIH	puruckerm@mail.nih.gov
Sudhir Raju	Rockville, MD	sraju@ctisinc.com
Dr. Louise Ramm	NIH	RammL@mail.nih.gov
Tracy L. Rankin, Ph.D.	NIH	rankint@mail.nih.gov
Alex R. Razzook, M.S.E.	Washington, DC	arazzook@gmail.com
Gregory Reaman, M.D.	COG	greaman@childrensoncologygroup.org
Dr. Karin A. Remington	NIGMS	remingka@nigms.nih.gov
Dr. Kyu B. Rhee	NIH	rheekb@mail.nih.gov
Leslie Rider-Araki	Westat	leslierider@westat.com
Dr. William Riley	NIH	wiriley@mail.nih.gov
Rex R. Robison	NIH	rexr@nih.gov
Carmen L. Rosa	NIH	crosa@nida.nih.gov
Dr. Yves D. Rosenberg	NIH	rosenbey@nih.gov
Dr. Daniel Rosenblum	NIH	rosenblumd@mail.nih.gov
Michael Rosenthal, MD	Dept. of Family & Community Medicine	michael.rosenthal@jefferson.edu
Charlie O. Roth	NIH	mainciaman@gmail.com
Domenica Rubino, MD	Falls Church, VA	drubino@rocketmail.com
Dr. Hubert K. Rucker	Meharry Medical College	hrucker@mmc.edu
John G. Ryan, Dr.P.H.	ePCRN	johngryan@miami.edu
Dr. Jody Sachs	NIH	sachsjg@mail.nih.gov
Dr. Leila G. Saldanha		lgs@nutriq-llc.com
Dr. Michael H. Sayre	NCRR	sayrem@mail.nih.gov
Alan N. Schechter, MD	NIH	aschecht@helix.nih.gov
Barry Schmetter	NIH	schmetterb@nhlbi.nih.gov
Dr. Kendra Schwartz	Wayne State University	kensch@med.wayne.edu
Branka Sekis	Silver Spring, MD	bsekis@s-3.com
Jose Serrano, MD	NIH	js362q@nih.gov
Katherine M. Serrano	NIH	serranok@mail.nih.gov
Joanne Severe	DSIR, NIMH	jsevere@mail.nih.gov
Dr. Hasnaa Shafik	NIH	shafikh@mail.nih.gov
Mehul Shah	Rockville, MD	mshah@ctisinc.com

Contact	Program/Affiliation	Email
Sheetal Shah	NIH	shahsheetal@mail.nih.gov
Dr. Pushpa Sharma	Critical Care Decisions	psharma@usuhs.mil
Celia Sharp		celia.sharp@comcast.net
Dr. Sheryl Sherman	NIH	shermans@nia.nih.gov
Jeff Shilling	NIH	jdshilling@nih.gov
Nancy Shinowara, PhD	NICHD/NCMRR	shinowara@nih.gov
Dr. Shy Shorer	NIH	shorers@niaid.nih.gov
Keisha L. Shropshire	NIH	kshropsh@mail.nih.gov
Dr. Susan B. Shurin	NHLBI/NIH	shurinsb@nhlbi.nih.gov
Hilary D Sigmon, PhD, RN	NIH	hilary.sigmon@nih.gov
Dr. Jonathan C. Silverstein	UChicago/Argonne Computation Institute	jcs@uchicago.edu
Dr. Ida Sim	ePCRN	ida.sim@ucsf.edu
Hua-Chuan Sim, MD	NIH	simh@mail.nih.gov
Dr. Julia Slutsman	NIH	slutsmaj@mail.nih.gov
Dr. Robert A. Smith	NIH	smithra3@nhlbi.nih.gov
John A. Smith	NIH	johnsmith@ventera.com
Namara Smith	AABB	nsmith@aabb.org
Dr. Charles Sneiderman	NIH	charlie@nlm.nih.gov
Dr. Scott Somers	NIGMS/NIH/GOV	somerss@nigms.nih.gov
Dr. George Sopko	NIH	sopkog@nih.gov
Stuart M. Speedie, PhD	ePCRN	speed002@umn.edu
Vivian Speer	CTN Best Practices	vspeer@RemedyMD.com
Richard C. Steinman	Intertrial	rcs6@columbia.edu
Dr. Mark Stephens	USU-FAP	mstephens@usuhs.mil
Dr. Paul S. Strumph	New York, NY	pstrumph@jdrf.org
David Sturgill	NIH	davidsturgill@niddk.nih.gov
Meryl Sufian	OPASI/EB	sufianm@mail.nih.gov
Dr. Margaret Sutherland	NIH	sutherlandm@ninds.nih.gov
Kathy Sward, MD	NIH	kathy.sward@nurs.utah.edu
Dr. Betty Tai	NIH	btai@nih.gov
Dr. Bernard Talbot	NIH	talbotb@mail.nih.gov
Tina P. Tan	GEORGETOWN	tpt6@georgetown.edu
Dr. Irena Tartakovsky	Washington, DC	itartakovsky@aamc.org
Anne S. Tatem, MPA	NIH	tatema@mail.nih.gov
Dr. Kristina D. Thiagarajan	NIH	thiagarajakd@ornl.gov
Ella E. Thompson	HMORN CCSN	thompson.e@ghc.org
Dr. Syed Tirmizi	Silver Spring, MD	syed.tirmizi@hq.med.va.gov
Anne Tompkins	NIH	tompkinsa@mail.nih.gov
Dr. Anne Trontell	AHRQ COE	anne.trontell@ahrq.hhs.gov
William Tulskie	Rockville, MD	btulskie@ctisinc.com
Christine Ulbricht	NIH	uchristi@mail.nih.gov
Patricia Valente, MD, MBA	NIH	PValente@ctisinc.com
Don Vena	Rockville, MD	dvena@emmes.com
Pat Vermeersch, PhD, RN	Wright State University	patricia.vermeersch@wright.edu
Nelly E. Villacreses	NIH	Nelly248@hotmail.com
L. Vitkovic, Ph.D.	NIH	vitkovil@mail.nih.gov

Contact	Program/Affiliation	Email
Dr. Kishena C. Wadhwani	CTN Best Practices	kishena.wadhwani@ahrq.hhs.gov
Paul G. Wakim	NIH	pwakim@nida.nih.gov
Anita Walden	TB Trials Network	anita.walden@duke.edu
Madeleine Wallace	NIH	wallacem2@mail.nih.gov
Dr. Madeleine F. Wallace	NIH	wallacem2@mail.nih.gov
Dr. Carol A. Wallace	UNIV. WASHINGS	cwallace@u.washington.edu
Dr. Gwenyth R. Wallen	NIH	gwallen@cc.nih.gov
Robert L. Walsh	NIH	rwalsh@nih.gov
Dr. Marc Walton	FDA/HHS	marc.walton@fda.hhs.gov
Dr. Lan-Hsiang Wang	NIH	Lw72f@nih.gov
Dr. Philip Wang	NIH	wangphi@mail.nih.gov
Adam Wanner, M.D.	Miami, FL	awanner@med.miami.edu
Rita T. Wedig, PhD, RD, LD	Adm. Dir. Health Sci. Ctr. Res. Off	rita.wedig@Louisville.edu
Dr. Anita C. Weinblatt	Chevy Chase, MD	anita.weinblatt@gmail.com
Susanna Weiss, Ph.D., J.D.	NIH	Weisssu@niaid.nih.gov
Ellen M. Werner, PhD	NIH	wernere@nhlbi.nih.gov
Dorothy West, M.P.H.	NIH	westd@mail.nih.gov
Buddy West	CTN Best Practices	buddy.west@duke.edu
Mary L. Westcott, Ph.D.	NIH	mwestcot@mail.nih.gov
Dr. Barbee Whitaker	AABB	bwhitaker@aabb.org
Kenneth White	Silver Spring, MD	mjackson@s-3.com
Dr. Betsy L. Wilder	NIH	betsywilder@nih.gov
Samantha E. Williams	NIH	williamss3@mail.nih.gov
Joan Williams	NIH	jwilliamsm@cc.nih.gov
Robert Williams, MD, MPH	RIOS Net	rlwilliams@salud.unm.edu
Marc Wine	Ft. Detrick, MD	wine@tatrc.org
Dr. Sukyung Woo	NIH	woos@mail.nih.gov
Jonelle Wright, PhD	Miami, FL	Jonelle@miami.edu
Anne P. Wright	NIH	awright@circlesolutions.com
Dr. Ashley Y. Xia	NIH	axia@niaid.nih.gov
Dr. Chunlin Xiao	NIH	chunlin.xiao@appliedbiosystems.com
Dr. Liming Yang	NIH	lyang@mail.nih.gov
Dolly T. Yang, MPH	COG	dyang@childrensoncologygroup.org
Dr. Alison Yao	NIH	yaoal@niaid.nih.gov
Dr. Barbara P. Yawn	Olmsted Medical Center	byawn@olmmed.org
Dr. Jane Ye	NIH	yej@mail.nih.gov
Joan Young	Rockville, MD	jyoung@pdsa.org
Dr. Vilma Yuzbasiyan-Gurkan	Michigan State University	yuzbasiyan@cvm.msu.edu
Richard Zimmerman, MD MPH	Family Medicine, University of Pittsburg	zimmer@pitt.edu