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

2nd Steering Committee Meeting
Summary Dated: August 3, 2005

May 9 and 10, 2005
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TABLE OF CONTENTS

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Chairperson: James P. Kiley, Ph.D., Director, Division of Lung Diseases, NHLBI, NIH

Organizational Co-chair: Dr. Jody Sachs, NHLBI Project Officer

Final Report: July 26, 2005

1.0 Steering Committee Meeting Goals

The 2nd Steering Committee Meeting was conducted on May 9 – 10, 2005, at Natcher Conference Center on the NIH Main Campus in Bethesda, Maryland. This document represents the summary and recommendations from the Steering Committee membership. The meeting was jointly conducted by NHLBI and the University of Pennsylvania Coordinating Center. The purpose of the meeting was to enhance group discussion and information sharing among the Roadmap programs, particularly those involving informatics initiatives. Specific areas covered during the meeting included presentations from several trans-NIH collaborative initiatives and a brief review of progress from the twelve program investigators. Approximately 52 people attended including investigators and information technology participants and Institute members. The primary emphasis focused on research network development and informatics. In section 1.1 an executive summary and meeting recommendations are presented.

1.1 Executive Summary

The roadmap programs are making progress toward their stated objectives. Several NIH initiatives were presented during this meeting that can support and provide information and expertise to the roadmap program investigators. In order to enhance the efficiency of all of the networks it is important for all of the program participants to collaborate within the working groups to address the common themes among the programs. By the end of the year, the groups should be able to report significant progress in their individual programs as well as be able to pool resources among working groups to contribute to common infrastructure elements, particularly in the area of clinical research informatics. The next Steering Committee meeting in December 2005 will provide roadmap investigators the opportunity to demonstrate the advancement achieved within and among the programs.

2.0 Roadmap Background

Clinical research has been the linchpin of this nation's biomedical research enterprise. Yet clinical research has become increasingly difficult to do, and it has become clear to the scientific community that the United States must recast its entire system of clinical research if such efforts are to remain as successful as they have been in the past.

To accelerate and strengthen the clinical research process, a set of NIH Roadmap initiatives will work toward improving the clinical research enterprise by adopting a systematic infrastructure that will better serve the evolving field of scientific discovery. This effort, which complements the other initiatives that comprise the NIH Roadmap, will provide the necessary foundation for advancing basic and clinical research. With the NIH Roadmap in action, investigators will be better poised to translate basic discoveries into the reality of better health for our nation.

Several initiatives are in place to carry forward this goal:

- Clinical Research Networks and NECTAR
- Clinical Research Policy Analysis and Coordination
- Clinical Research Workforce Training
- Dynamic Assessment of Patient-Reported Chronic Disease Outcomes
- Translational Research

2.1 Organizational Structure of Clinical Research Network Roadmap Project
Presenter: James P. Kiley, Ph.D.

Project activities and objectives are diverse; however, they have common elements which would benefit from a coordinated approach and overarching structure. Organizational options include (i) each contract proceeding individually or (ii) establishing some coordinating structure. Gains are possible through collaboration with resources available across institutes.

Discussion Points:

- Thematic clusters are evident that may form the basis for working groups.
- While important thematic clusters are evident, some important themes may be completely missing. Clinical research informatics is a common theme among the programs.
- Consider the best model of interaction and cooperation, even if investigators did not include funding required to support a model of organized cooperation.

2.2 Trans-NIH Roadmap Networks Coordinating Committee
Presenter: James P. Kiley, Ph.D.

The Trans-NIH Roadmap Networks Coordinating Committee provides an opportunity for the NIH to take the output from the individual Roadmap contracts back to the many Institutes to enable access to the results and to benefit from this infrastructure.

NIH is interested in facilitating cooperation of the Roadmap contracts via this Committee. All Investigators should feel free to contact Committee members to discuss pertinent issues.

2.3 Data Safety Monitoring / Security Plan
Presenter: James P. Kiley, Ph.D.

Monitoring is required for intervention projects and should capitalize on existing local structures such as institutional IRB, or DSMB. The institute will not establish oversight or protocol review committees for studies or feasibility projects.

Each investigator should contact the chairperson of the existing monitoring committee or work with the study Project Officer. The investigator should outline a plan regarding how that committee will work with incorporating the Roadmap aspect of the project, document this information and send to the NHLBI Project Officer. These plans were submitted in December 2004.

Discussion Points:

- It was suggested for those projects that do not require an institute level oversight board that investigators provide a plan for monitoring activities encompassed by their Roadmap contracts in accordance with the template structure under NHLBI. http://www.nhlbi.nih.gov/funding/policies/dsm-12.htm
- Security plan template, that is linked on the NHLBI public website: http://irm.cit.nih.gov/security/secplantemp.doc

2.4 University of Pennsylvania Coordinating Role
Presenter: J. Richard Landis, Ph.D.

Dr. Kiley introduced Dr. Richard Landis and explained that the University of Pennsylvania will serve in an administrative and logistical coordinating capacity. This role will continue to evolve over the course of the study. Dr. Kiley indicated that more activity and responsibility can be requested of the University of Pennsylvania if required (e.g., conference call coordination for Working Groups).

Discussion Points:

Dr. Kiley asked the Investigators to identify any other coordinating activities that might be required. The following activities were identified:

- Roadmap Web Site – An award for the Roadmap website was made to the University of Pennsylvania Clinical Research Computing Unit. The website will have public and private

access, links to NIH roadmap site and other modules to be determined. Dr. Kiley emphasized that it is very important for the public to 'see and hear' about the Roadmap activities being undertaken via the Roadmap contracts.

- Chair and Co-Chair - Decisions regarding overall study governance and nomination of a chair person were deferred pending better definition of the coordinating agenda and mission statement. Discussion included rotation of leadership.

3.0 NIH Roadmap Projects

NIH Roadmap: Re-engineering the Clinical Research Enterprise: Clinical Research Networks & NECTAR will promote and expand clinical research networks that can rapidly conduct high-quality clinical studies that address multiple research questions. An inventory of existing clinical research networks will explore existing informatics and training infrastructures in order to identify characteristics that promote or inhibit successful network interactivity, productivity and expansion, or broadening of research scope. "Best practices" can then be identified and widely disseminated, further enhancing the efficiency of clinical research networks.

In the Clinical Research Networks & NECTAR initiative, the NIH will promote the creation of better integrated networks of academic centers that work jointly on clinical trials and that include community-based health care providers who care for sufficiently large groups of well-characterized patients. Implementing this vision will require new ways to organize the way clinical research information is recorded, new standards for clinical research protocols, modern information technology, and new strategies to strengthen the clinical research workforce.

3.1 Opening Session: Overview of Re-Engineering Clinical Research Enterprise Presenter: Dr. Stephen Katz

Dr. James Kiley introduced the new NHLBI Project Officer of this Roadmap initiative, Dr. Jody Sachs. Dr. Stephen Katz (NIAMS, NIH) reiterated the major Roadmap foci: (i) new pathways for discovery, (ii) interdisciplinary teamwork, and (iii) clinical research networks. All initiatives emphasize infrastructure development. The following clinical research activities were described:

- Translational Research I is focused on Research Cores for small molecule development. These Cores are modeled on the NCI RAID.
- Translational Research II is focused on three types of regional Translational Research Centers. These Centers are intended to provide research support services.
- Clinical Research Work Force Training.
- Clinical Research Network and NECTAR.
- Goal is best use of government funding for developing common clinical research network infrastructure, including clinical research informatics.
- Patient-Reported Outcomes Measurement Information System (PROMIS) will support an integrated approach to data collection and management.
- Harmonization of Regulatory Requirements.

Dr. Katz stated:

- There is dedication to the goal of discovering the best methods for clinical research network expansion.
- The NIH is interested in taking the output from the Roadmap contracts and making use of the information and results.
- To involve junior investigators in academic research, the Institute has engaged in discussions with the Deans of several medical schools and will meet with the Association of Academic Health Centers in May 2005. Identifying a home for clinical research will foster this growth.
- The Institute will not dictate what occurs at academic health centers as that will vary among centers, though the roadmap focus on translational research from the bench and bedside in academic health centers into the community will enhance this aspect of clinical research.

3.2 Supporting Clinical Research with Information Technology
Presenter: Stephen Rosenfeld, MD, MBA, Department of Clinical Research Informatics

Dr. Rosenfeld described the CRIS vision of Integrated Clinical Research Workflow. A primary objective is to work for point of care integration of clinical care and research data acquisition. Concern was expressed regarding obtaining consent to use and transfer data in ways not yet described. This is a policy issue that the use of the standard security model may help address. The group discussed the following common research operational problems.

- Enrolling patients in sequential trials is a problem because of the lack of standardization in eligibility criteria. Data collection systems should strive to collect and evaluate a larger set of common data elements. Patients are identified by systems, investigators and by people identifying studies.
- In many studies, data quality is problematic. Data extraction from medical record to CRF is several steps removed from the source. To improve data quality, researchers should aim to design data collection systems that are less intrusive and not focused on ergonomics and work flow.

3.3 BIRN Initiative: Biomedical Informatics Research Network
Presenter: Elaine Collier, MD, NCRR

Dr. Collier introduced Biomedical Informatics Research Network (BIRN) which is an NIH initiative that fosters distributed collaborations in biomedical science by utilizing information technology innovations. Currently the BIRN involves a consortium of 19 universities and 26 research groups that participate in one or more of three test bed projects centered on brain imaging of human neurological disorders and associated animal models. The following additional information was discussed:

- BIRN, which uses Internet 2 as the backbone and informatics tested in neurological research, is an information infrastructure project, not a neurological research initiative.
- Image data basing: uses special program to de-identify MRI scans that can render data anonymous by “de-facing” the scan image without affecting the brain elements of the scan. This information database contains scan image results and includes mouse brain data.
- BIRN coordinating center supports research infrastructure development including database query support.

The future direction of BIRN is:

- Extension to other research institutions interested in neuro-imaging, etc., by making web portal available to other institutions and investigators. A policy will be developed to govern sharing of tools and data among participants in the near future. Presently, issues of intellectual property are dealt with inside the network.
- Extension of research infrastructure model to other therapeutic areas.
- Partnering with informatics projects to enhance interoperability.
- www.nbirn.net

3.4 caBIG: Cancer Bioinformatics Grid
Presenter: Ken Buetow, MD, NCICB, NCI

The *ca*ncer *B*iomedical *I*nformatics *G*rid, or */caBIG™/*, is a voluntary network or grid connecting individuals and institutions to enable the sharing of data and tools, creating a World Wide Web of cancer research. The goal is to speed the delivery of innovative approaches for the prevention and treatment of cancer. The infrastructure and tools created by caBIG™ also have broad utility outside the cancer community. caBIG™ is being developed under the leadership of the National Cancer Institute's Center for Bioinformatics <http://ncicb.nci.nih.gov>. The group discussed the utility of the caBIG tools and infrastructure, outside of the cancer community.

The goal of caBIG is to create a virtual web of data, individuals and organizations to support and better enable collaborative research, to develop common infrastructure, data elements, and data models in order to provide raw scientific data to the research community and facilitate integration of data. They have identified three domain workspaces: clinical trials management systems, integrative

cancer research, tissue banks and pathology. Three strategic planning groups have been formed to assist with development activities: data sharing and intellectual capital, training, and caBIG strategic planning.

Deliverables:

- Study assistance: eIND filing/reporting, eManagement of clinical trials, integration of diverse trials
- Tissue management system
- Plug and play tools (microarray, proteomics, pathways, etc.)
- Diverse library of information noted above
- CaCORE - Cancer common ontologic representation environment INCLUDING biomedical objects, common data elements, controlled vocabulary; working with HL7 & CDISC for common standards on protocol elements.
- Data Standard Repository (caDSR) includes libraries of standard CRF modules/elements.
- Website: https://cabig.nci.nih.gov/

3.5 WESTAT: Inventory and Evaluation of Clinical Research Network (IECRN)
Presenter: Stephen Durako

This proposal is to conduct an Inventory and Evaluation of Clinical Research Networks in response to RFTOP 169. The three major goals of the project are to (1) develop an inventory and database of clinical research networks; (2) prepare a detailed description of existing practices and assessment of best practices; and (3) conduct a national leadership forum on the results of the inventory and assessment studies. This project is part of the NIH Roadmap to improve the speed and effectiveness of translating basic scientific discoveries into clinical products and practices that improve health care. In particular, this project is related to Re-engineering the Clinical Research Enterprise. One objective of the re-engineering process is to enhance the efficiency and productivity of clinical research by promoting clinical research networks to rapidly conduct high quality clinical studies where multiple research questions can be addressed.

This project will be performed by a team that includes Westat (prime contractor), Social and Scientific Systems (SSS), Aspen Systems, and TeraQuest Metrics. In addition, we have assembled an Advisory Panel of leaders from a variety of current clinical research networks. The Advisory Panel will: (1) provide initial input about what are considered the most important questions to study and issues to address in developing best practices for clinical research networks; (2) assist with identification of research networks; (3) provide legitimacy to our efforts and assist in obtaining cooperation from network representatives; (4) review findings and suggestions for best practices before they are presented in a national forum; and (5) serve as leaders in disseminating and implementing best practice recommendations in the clinical research networks.

This project will be under the corporate leadership of Mr. Stephen Durako, Westat Vice President and Director of Westat's Clinical Trials Area. The Westat team's co-investigators will be Jonas Ellenberg, Ph.D. and George Schreiber, Sc.D. The project director will be Nancy Dianis, M.S.N. Susan Berkowitz, Ph.D., and Darcy Strouse, Ph.D., are experienced evaluation methodologists who will lead the design, development, conduct, and analysis of the evaluation.

The Westat team will take an integrated, carefully sequenced, three-tiered approach to meeting the study objectives, in which each tier informs and builds upon the other. In Tier **1: Develop an inventory and database of all (150) clinical research networks**, we will identify and obtain basic information about as many existing clinical research networks as possible. In tandem, we will design and create a flexible database containing basic characteristics of all the identified networks along with an accompanying user-friendly web site. In Tier **2: Design and implement a survey to describe existing practices in a representative group of one-third (50) of all networks**, we will conduct a mixed-mode semi-structured survey of approximately 50 clinical research networks. The sample will represent a range of network types and models based on grouping data from the inventory of 150 networks. Compared to the inventory**,** the survey will obtain more complete data on existing practices across multiple realms of network organization and operations (e.g., management and governance; informatics infrastructure, training) as well as facilitators and impediments to network success in these realms. In Tier **3: Identify and assess in depth a subset of networks showing promise of**

"best practices", we will select a subset of networks with candidate "best practices" in one or more of the key realms. Teams will conduct 4- to 5-day site visits to selected network locations, applying rapid ethnographic assessment techniques including in-depth interviews, observations, document review, focus groups, and, when applicable, a specialized methodology for evaluating informatics. The planning and conduct of a National Leadership Forum represents the culmination of all data collection and analysis activities in Tiers 1, 2, and 3. The Forum will be our opportunity to present the results of these intensive efforts and will involve working in close conjunction with NIH to develop a plan for how to do so most effectively in order to further the aims of the roadmap.

Mr. Durako stated that the IECRN is intended to 'take a snapshot of what currently exists' in the clinical research arena. This project was not funded in response to BAA.RM.04.023 but was will proceed in parallel to all awarded Roadmap contracts. This project will identify best practices through contact with the awarded Roadmap contracts. Interested members should plan to participate in the National Forum Meeting during which this information will be formally presented.

Currently the project has identified 260 CRNs; 50% of which are clinical trial networks, though not all CRNs met the definition for inclusion in this inventory phase. The project is proceeding as scheduled and is beginning to implement Phase 3 of the program. The phases are described below.

- Phase 1: surveying CRNs
- Phase 2: review and evaluation of CRNs
- Phase 3: describe best practices
- Phase 4: national forum to discuss best practices (tentatively in May, 2006)

3.6 AHRQ Integrated Delivery System Research Network (IDSRN)
Presenter: Cynthia Palmer, MSc.

The Agency for Healthcare Research and Quality (AHRQ) is a research agency that works to ensure that providers use evidence-based research to deliver high-quality health care. The agency's mission is to improve the quality, safety, efficiency, and effectiveness of healthcare for all Americans by bringing research to the benefit of patient care. Translation of Research into Practice (TRIP) requires a strategic approach to assure that research findings are ready to be used, widely available, and actionable.

4.0 Coordinating Informatics - Group Discussion

The twelve Roadmap programs have a common theme that focuses on improving the efficiency and applicability of their clinical research infrastructure, thereby increasing the scope and collaborative capabilities, by expanding and standardizing the informatics infrastructure within the programs. Program members are working together and in collaboration with other NIH enterprises such as caBIG and BIRN, in a consolidated effort to identify and select the best methods and standards for informatics projects. The commitment and collaboration among researchers in the use of informatics tools will provide a common informatics platform to exchange data between disparate systems to support the research community.

These initiatives and the IECRN inventory will be the foundation for development of the National Electronic Clinical Trials and Research (NECTAR) network. The IECRN inventory of clinical research networks will explore existing informatics and training infrastructures in order to identify characteristics that promote or inhibit successful network interactivity, productivity and expansion, or broadening of research scope. NECTAR will provide the informatics structure that will serve as the backbone for interconnected and inter-operable research networks. This network will promote clinical research collaboration by utilizing information technology innovations enabling researchers to broaden their research scope. The efficiencies gained for clinical researchers will translate into efficiencies among the Institutes.

Relative to the presentations focusing on health information technology, the group discussed the following initiatives:

- The group agreed that it would like to collaborate with the NIH programs such as BIRN and caBIG. To facilitate what is occurring among programs and caBIG, contact Peter Covitz, NCI. Though in its infancy, caBIG is working with the UK as interface to the European Union and as

such will ultimately have international applicability. Dr. Sachs encouraged the group to also consider Industry sponsorship. The Clinical Research Information Exchange interest in this program will be determined in collaboration with the Institute.

- Intellectual Property sharing and material transfer agreements are generally bound by a contract which binds all members. The challenge of representing the entire community of research groups is inherent in this paradigm but there now exists representation.
- Alan Morris encouraged the group to complement the "top down" collaboration effort with "bottom up" effort, such as within the Roadmap programs.
- Messaging was described as adoption of standards and efficient incorporation of them into systems. It was described as most useful when connected to human use and purpose; less focus on technology and more on reference implementation. Eventually this model may be expanded to address clinician/patient interaction to reduce variation in clinical care. Focus should be on operationalizing appropriate choices.
- Mapping standards are being developed to support migration from HL7 Version 2 to Version 3. Toolkit is available.

5.0 CRNs and NECTAR Programs

The following are funded programs of the Clinical Research Networks & NECTAR initiative:

MCRC	An Integrated Academic-Community Research Enterprise
AGNIS	A Public System for Electronic Exchange of Clinical Network Data
TB Trials Network	Enhancing the U.S. Public-Health System's Willingness and Capacity to Engage in Clinical Research
CTN Best Practices	Creating, Implementing, and Sharing Best Practices for Clinical Trial Networks
Intertrial	Clinical Trial Network Infrastructure and Collaborative Technology
CNICS	Integrating HIV Resistance Data into the CNICS Cohort
CRN Harmony	Harmonizing NIH and Industry Sponsored Clinical Research Network Architecture
HMORN CCSN	Coordinated Clinical Studies Network (CCSN)
Critical Care Decisions	Re-engineering Clinical Research in Critical Care
ePCRN	The electronic Primary Care Research Network (ePCRN)
COG	Developing a Collaborative Effort between the Pediatric Blood and Marrow Transplant Consortium (PBMTC) and the Children's Oncology Group (COG)
RIOS Net	Research Involving Outpatient Settings Network (RIOS Net) and Underrepresented Populations

5.1 MCRC: "An Integrated Academic-Community Research Enterprise" - The Michigan Clinical Research Collaboratory, Principal Investigator: Daniel J. Clauw, M.D.

Aim #1:	*Re-engineer clinical research in Michigan by integrating well-functioning primary care research networks, academic research centers of excellence, and a center dedicated to supporting clinical research*
Aim #2:	*Develop a new, tailored informatics system to address and integrate the unique needs of this re-engineered network*
AIM #3:	*Demonstrate that the re-engineered network can successfully design, conduct and rapidly translate clinical investigations that focus upon highly prevalent, vitally important, but currently neglected co-occurring clinical diseases*

Disseminate findings, tools, and strategies from this project to other networks and ultimately, NECTAR. This proposal describes a technical work plan that will integrate clinical research centers of

excellence with established community primary care networks to create a new enterprise. Only then, will the effectiveness of cutting-edge research advances be tested in real-life settings; only then will community physicians develop a sense of "ownership" of results and translate research advances into their practices; only then will common co morbidities be addressed in real-life settings; and only then will the findings of primary care clinicians and research networks be re-translated bidirectionally. Specifically, 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).**

The central "hub" of the MCRC will be the University of Michigan **Center for the Advancement of Clinical Research (CACR).** CACR is a unique unit that provides infrastructure and support for clinical research at the University of Michigan. CACR personnel have extensive experience in all facets of clinical research necessary for such re-engineering, including: 1) **Clinical Research Informatics Core** that has developed an in-house software program (BioDBx) that successfully runs large numbers of clinical research protocols; BioDBx will be re-engineered for expanded use, compatibility with other systems, and enhanced security; 2) **Project Management and Monitoring Core** that serves as the Data Coordinating Center for several NIH multicenter trials; 3) **Education Core** that focuses on educating physicians and other study personnel in clinical research practices; 4) **Research Development Core** that helps investigators with study ideas convert these into high quality protocols; and *5)* **Biometrics and Outcomes Resources Core** that provides biostatistical support.

Re-engineering the "human" processes will involve meeting with stakeholders from each of the networks to: 1) identify and / or develop common processes and languages that all three groups find acceptable, do not impede practice workflow and encourage active participation of their network physicians; 2) insure that re-engineered processes meet regulatory and compliance standards and are inherently efficient; 3) develop QI-based rollout and improvement programs for rapid integration of the networks; 4) develop a work plan to implement the feasibility project in all three networks, demonstrate the value of participation, disseminate and evaluate new approaches, and train a new generation of interdisciplinary / translational investigators. Interdisciplinary team leaders have already begun the processes and endorsements have been obtained.

The IT re-engineering is also underway, being directed by a Steering Committee of network physicians, Directors of the Research Centers, and Bioinformatics faculty. In the first year of funding this project will complete the development of an Honest Broker system that will enable the best of all existing IT systems to be maintained while introducing secure and HIPAA-compliant inter-operable interfaces. Mapping, data standards, and linkages with patient registries will follow. Year 02 will complete gating mechanisms, BioDBx interfaces with M-CORPP from the Cardiovascular Center and M-CORE from the Depression Center, and the beginning of the feasibility project. Year 03 will complete the roll-outs, interfaces, and overall testing in all three primary care and the two specialty centers. The successes and failures of these new processes and systems will be clear by the completion of the feasibility project; modifications and refinements will be implemented as required.

This re-engineered MCRC is designed to achieve an open-source, inter-operative enterprise, providing effective interfaces among traditional research silos, catalyzing interdisciplinary research, fostering prompt bidirectional translation, educating a new generation of interdisciplinary investigators, and developing and disseminating standards with potential value for ongoing national efforts such as NECTAR.

Dr. Greden provided an update to the MCRC and described the next steps for the program which are to integrate the primary care research networks, academic CRN, and Research Center (depression center), utilize the web portal for bulletin board, consent, registry and recruitment capabilities, unify IRB review capabilities and the continued development of "Honest Broker" of information ensuring privacy. (Honest Broker is a clinical information to research system with honest broker oversight of the data transfer and privacy management).

5.2 AGNIS: "A Public System for Electronic Exchange of Clinical Network Data" - A Collaborative Effort of the IBMTR and the NMDP", Principal Investigator: Dennis L. Confer, M.D.

Aim #1:	*Increase the scope of network activities between multiple clinical networks supporting hematopoietic stem cell (HSC) transplantation*
Aim #2:	*Increase network participation, including training, facilitating easy entry of new sites, acquisition of additional patient and investigator participation*
Aim #3:	*Facilitate network communication and cooperation by developing new approaches and tools for electronic data exchange.*

The National Marrow Donor Program ® (NMDP) and the Medical College of Wisconsin's International Bone Marrow Transplant Registry (IBMTR) are pleased to collaborate in this response to RAA-RM-04-23. "Re-Engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks." Our proposal, "A Public System for Electronic Exchange of Clinical Network Data: A Collaborative Effort of the IBMTR and the NMDP," supports the Technical Objectives to 1) Increase the scope of network activities between multiple clinical networks supporting hematopoietic stem cell (HSC) transplantation; 2) Increase network participation, including training, facilitating easy entry of new sites, acquisition of additional patient and investigator participation; and 3) Facilitate network communication and cooperation by developing new approaches and tools for electronic data exchange. An important aspect of this proposal is its open source spirit, that is, all work products developed under this project will be made publicly available to facilitate adoption, adaptation, extension and improvement in our and other networks.

The first aim of this study is 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.

Implementation of clinical data exchange will include:

- A messaging exchange between 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,

Based upon these specific aims, we have developed a series of six specific tasks that comprise the work plan for this proposal. For each of the tasks, we present the descriptions of the activities to be performed, the methodologies for accomplishing these activities and a discussion of anticipated difficulties. A major strength of our plan is the governance structure that we have envisioned, which combines the clinical and scientific skills of an expert, internationally constituted Advisory Committee with the bioinformatics knowledge of a Technical Committee. An Executive Committee, comprised of the lead investigators in this proposal, will receive guidance from these two working committees and oversee the enterprise.

This program has conducted several national and international meetings to support the public system for electronic exchange of clinical network data as a collaborative effort of the Center for International Blood and Marrow Transplant Research (CIBMTR) and the NMDP and the EMDIS European Marrow Donor Information System. The program has established a technical committee to collaborate to

seek solutions for sharing blood and marrow transplant data. Efforts to engage leaders in developing this initiative include providing a stipend and scheduling AGNIS meeting to coincide with major BMT meetings.

5.3 TB Trials Network: "Enhancing the U.S. Public-Health Systems Willingness and Capacity to Engage in Clinical Research" - Duke University Medical Center, Principal Investigator: Carol Dukes Hamilton, M.D.

Aim #1:	*Engage public health leaders in the clinical research enterprise in general, and TB clinical research in particular, by investing them in priority-setting forums that will also help the TBTC to create a relevant, timely and dynamic future scientific agenda*
Aim #2:	*Identify and reduce barriers to clinical trials research in U.S. public health clinics*
Aim #3:	*Develop, with public health leaders and networks engaged in multicenter trials, a model for improving the process of human subjects protection review in multicenter trials*
Aim #4:	*Create an interoperable, secure web-based electronic data capture system for the TBTC, that will interface with public health surveillance systems*

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.

We will accomplish our goals by collaborating with an established academic research organization, the Duke Clinical Research Institute (DCRI), using their infrastructure, their clinical trials expertise and tools, and their established and developing training programs. The objective of the TBTC-DCRI are to:

Engage public health leaders in the clinical research enterprise in general, and TB clinical research in particular, by investing them in priority-setting forums that will also help the TBTC to create a relevant, timely and dynamic future scientific agenda: We will bring together public health leaders and academic, foundation and pharmaceutical company-based investigators to consider priorities, timelines and needed resources for high priority projects. Fundamental to this process will be identifying public health priorities, and obtaining their intellectual commitment to the clinical research process.

Identify and reduce barriers to clinical trials research in U.S. public health clinics: We will work with representative TBTC-associated public health clinics to identify the most significant barriers to conducting clinical research in their setting and develop a responsive strategy to reduce the barriers. We will measure the success of our intervention by comparing enrollment before and after the intervention, as well as by comparing enrollment among matched sites with and without the intervention.

Develop, with public health leaders and networks engaged in multicenter trials, a model for improving the process of human subjects protection review in multicenter trials: We will work with members of the public health community, with multicenter trialists, and with ethicist who focus on "human subjects protection" to address 2 specific issues. We will explore the impediments to expanded use of central IRBs in multicenter trials, and address the complexities associated with informed consent among subjects who do not speak English.

Create an interoperable, secure web-based electronic data capture system for the TBTC that will interface with public health surveillance systems: Our focus will be to design a system that is compatible with the national infrastructure being deployed in state and territorial networks of public

health. We propose ways to leverage ongoing surveillance data collection to improve our ability to recruit subjects to clinical trials, as well as compare trial populations with the population at large, so there will be a measure of the applicability of findings.

Dr. Hamilton described the formation of a TB Trials Consortium public health leadership team, a core leadership team and plans for a research symposium. The "barriers to research team" has surveyed TBTC site to determine site metrics and characterize them for inclusion in planned focus groups. The IRB team is conducting a survey of IRBs. In addition, the group is developing an EDC system for the TB Trials Consortium, developing a website and initiating implementation of NEDSS.

5.4 CTN Best Practices: "Creating Implementing, and Sharing Best Practices for Clinical Trials Networks" - Duke Clinical Research Institute, Principal Investigator: Robert A Harrington, MD, FACC, FSCAI

Aim #I:	*Implement programs and tools focused on building site capability with the ultimate goal of enhancing the recruitment, retention, and performance of clinical research sites.*
Aim #2:	*Develop a model for establishing common data elements and controlled terminology for cardiovascular disease and depression through a new partnership with the clinical data interchange standards consortium (CDISC).*
Aim #3:	*Create and implement a proposal development system to solicit and bring the best ideas for research questions from initial concept to execution in the most efficient fashion, including preparation suitable for government, foundation, or industry funding, with a focus on encouraging public/private partnerships.*
Aim #4:	*Develop a network informatics infrastructure that can be applied and used across multiple networks and provide an integrated electronic repository of tools and programs to assist the site in its study conduct activities while fostering communication across sites and networks.*

The need for a more efficient and effective approach to clinical research has been articulated by numerous public and private sources over the past several years. One of the greatest inefficiencies of the current model of clinical research in our country is the lack of a sustaining infrastructure (which includes shared resources, common data standards, and effective use of information technology among researchers), as well as the lack of a convenient forum to share best practices and learn from one another's mistakes and successes. The concept of a "network" is a step in the right direction toward advancing the nation's clinical research capacity. The operational efficiencies of a network of investigators, coupled with the scientific camaraderie that develops among researchers having similar goals and interests, should advance the field of clinical research.

We propose a customer management approach to interacting with network sites that will facilitate interoperable clinical research by enhancing site recruitment, training, performance, and accountability and by creating a sustained improvement in the efficiency and quality of the interaction between the clinical research subject and the investigator. This approach has four components: First, we will treat the clinical research site as a customer, creating a mechanism to define and share best practices designed to engage, support, and invest sites in research. We will build site capability by developing tools and programs to help them enhance their understanding and knowledge of clinical research. Second, we will use cardiovascular disease as a model for developing common data elements and standard terminology that can be shared among researchers and networks; this will prevent sites from spending their time relearning new nomenclature for each study and it will enhance interest in the research by making data sharing among studies easier. We will use depression as an example of cross-discipline interoperability. Third, we will engage the site in identifying and prioritizing important new research ideas and we will provide an infrastructure that enables networks to quickly take research ideas from concept to implementation.

Success will he measured by the extent to which the tools and programs developed are implemented by our networks, and the degree of participation of the sites in each of the networks. We will interview

and poll participants, asking for feedback regarding the success and usefulness of the tools. We will also share our results and experiences with other BAA awardees throughout the three-year contract.

The program has begun building capability for the recruitment, retention and performance of clinical research sites. It has engaged 50 DCRI cardiovascular sites. A successful kickoff meeting was held in March 2005. With regard to creating data standards, the group has begun collaboration through HL-7 working groups, describing the process flow and story-board planning. They have engaged ACC, AHA, ATS (American for Thoracic Society) leadership and ACC-AHA Joint Task Force on data standards. A stakeholders meeting is being held in May 2005.

Note: If required, Dr. Harrington can supply contract standard language that clarifies Duke's ownership or co-ownership of clinical trial database as well as standard language for publication committee for all publications resulting from the database with the guarantee that academic institution controls majority membership. This publication language was sound enough that it withstood a lawsuit by a device company trying to prevent publication of negative data.

5.5 INTERTRIAL: "Clinical Trial Network Infrastructure and Collaborative Technology" - Columbia University, Principal Investigator: Stephen B. Johnson, Ph.D.

Aim #1:	*Establish a flexible information infrastructure for clinical research, designed to enhance information flow, promote data sharing and reduce redundant effort;*
Aim #2:	*Develop a behavioral model of information technology use in clinical research, based on empirical study of information needs of users, barriers to technology use, and strategies for improving use;*
Aim #3:	*Promote research quality and encourage best practices through training, information technology for clinical trials, and collaborative technology to improve communication and cohesion.*

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.

The flexible information infrastructure will consist of software that manages the basic "transactions" of clinical research (e.g., scheduling a visit, or reporting physical exam values), in order to connect front-end user applications with back-end databases. Services provided by this infrastructure include automatic translation between different data coding schemes, pooling of common data to encourage reuse and reduce redundant effort, automated monitoring of protocol accruals, and automated matching of potential subjects to trials. This architecture allows multiple commercial and institutional applications to interoperate and provides researchers with real-time, access to research data via the creation of a virtual collaboratory.

Our approach is based on the observation that information technology in itself is insufficient to improve research processes; it is necessary to understand the behaviors that are required of all stakeholders, and the various factors that drive these. The research design will compare a number of

software tools in community and academic settings, and systematically contrast various educational interventions designed to promote usage. Software will be phased in over the three years, starting with simple, administrative tools in a few sites and expanding to more complex, clinical tools at a larger number of sites.

Dr. Johnson described aspects of the InterTrial program "Promoting best practices in a large community research network using scalable information systems," by highlighting the following information:

- Focus on community-based research utilizing assessment of behavioral aspects of involvement in clinical research and implementation of any process improvement efforts.
- Trying to "fuse" informational technology and behavioral science assessment of clinical trials abilities and processes.
- Promoting data sharing --- assess barriers; develop processes and systems to overcome barriers.
- Development of online Good Clinical Practice (GCP) training module focused on clinical research coordinators.
- Conduct of survey stakeholders, IT managers and clinical coordinators, using validated instruments as a method to assess site: "IT readiness," satisfaction with current site systems, computer literacy, and attitudes associated with use of computers as an important aspect of work. In addition, semi structured interviews were conducted. An observation visit was also conducted which involved shadowing of CRC (approximately 2 hours), assessing workflow processes and integration of technology into existing workflow.

5.6 CNICS: "Integrating HIV Resistance Data into the CNICS Cohort" - University of California - San Francisco, Principal Investigator: James Kahn, M.D.

Aim #1:	*To 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 to then upload the data into CNICS, an established research network.*
Aim #2:	*To 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 CNTCS database.*
Aim #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.*
Aim #4:	*Test and validate the utility of these tools built to store, transfer and analyze viral resistance data in the clinical research network.*

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 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 EMRs, to organize the data for clinical decision making, 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 research network 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.

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.

Dr. Haubrich provided an update of the program status, integrating HIV resistance data into the CNICS Cohort, and described the complex data transfer process required to upload into a central repository of data from CNICS, local and commercial laboratories. Several institutions such as UCSF, UCSD, UAB, UW, Harvard and CWRU are working to combine anonymized clinical data from primary care settings with electronic medical records to understand trends in the HIV epidemic (CFAR network).

5.7 CRN Harmony: "Harmonizing NIH and Industry Sponsored Clinical Research Network Architecture." - University of Pennsylvania, Principal Investigator: J. Richard Landis, Ph.D.

Aim #1:	*Develop Expert-Derived Clinical Research Network Re-Engineering Materials (CRN-REM),*
Aim #2:	*Establish Clinical Research Network Harmonization Methods Derived from Currently Merging NIH-Clinical Research Networks (two NIDDK-sponsored, multi-disease, multi-concurrent protocols, multi-center CRNs),*
Aim #3:	*Establish Clinical Research Network Harmonization Methods Derived from an Industry-Funded Partnership with an Academic Medical Center and Community-Based Practice Sites (first project undertaken is a large-scale, ten-year observational cohort study of rare pediatric disease outcomes),*
Aim #4:	*Integrate Emerging Clinical Research Network Re-Engineering Materials to an Existing, High-Visibility NIH Clinical Research Network (the NIDDK-sponsored Chronic Renal Insufficiency Cohort Study CRN), and*
Aim #5:	*Results Dissemination, Training, and Repeated Application (by the Office of Human Research, a responsibility ideally suited to this organization's role at the University of Pennsylvania).*

In response to BAA.RM.04.023, J. Richard Landis of the University of Pennsylvania (UPENN) Center for Clinical Epidemiology and Biostatistics (CCEB) is submitting this proposal entitled 'Harmonizing NIH and Industry Sponsored Clinical Research Network Architecture.' 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 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 scalable, prototypical, re-engineered research enterprise architecture for the conduct of clinical research within a broad-based frame work.

Dr. Landis described the progress of the Penn program by featuring the collaboration among a diverse group of Penn projects and divisions, encompassing industry, NIH and community based clinical research. The research team has established a library of data collection instruments, initiated collaborative development of standards and methodologies, and enhanced technology infrastructure to include the Oracle Clinical suite of applications.

5.8 HMORN CCSN: "Coordinated Clinical Studies Network (CCSN)" - Group Health Cooperative, Principal Investigator: Eric B. Larson, M.D.

Aim #1:	*Increase ability to respond to questions of national research interest*
Aim #2:	*Increase the pace that efficacious interventions are moved into practice*
Aim #3:	*Established an informatics platform to support research that will be among the most powerful worldwide in its scope and applicability to clinical practice*
Aim #4:	*Provide research opportunities and increased research interest among practitioners*
Aim #5:	*Provide project planning tools to streamline the budget and IRB review processes*
Aim #6:	*Create best practices for distributed data models*

We propose to develop the Coordinated Clinical Studies Network (CCSN), an unparalleled research facility for clinical and health services research that builds on the current capacity of the HMO Research Network (HMORN). The HMORN is a national network of leading research centers committed to undertaking collaborative, public-domain research to improve the practice of health care in the United States. HMORN member sites are uniquely positioned within some of the largest, most representative, and most innovative U.S. health plans. HMORN member plans provide comprehensive services in every US region ranging from prevention to palliation, to a defined population of 13 million people or 4% of the US population.

The HMORN is an ideal setting for answering the translational research questions posed by Haynes [1999]:

Does an intervention work?

Will it work in practice?

How much will it cost?

The infrastructure we propose will dramatically increase our 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. To that end, we will add to existing capacity of the HMORN in the areas of project planning and development, project implementation, systematized data collection and monitoring, project closeout and post-study surveillance, and dissemination including translation where appropriate.

The CCSN will support the full range of research that HMORN members regularly conduct, which includes cancer, infectious and chronic disease surveillance, health services and health economics research, behavioral, mental health and substance abuse studies, genomic research, complementary and alternative medicine, dental research, pharmacoepidemiological and pharmacoeconomic investigations as well as analyses of systems change and organizational behavior. Our unique status within the integrated health systems that sponsor our centers has also allowed HMORN researchers to establish a particular expertise in translational research and the CCSN will allow our ongoing successful efforts to translate research into practice.

We have proposed a set of deliverables designed to build and sustain a research infrastructure, but the primary measure of our success will be the number of clinical trials supported by the CCSN infrastructure developed under this BAA. A main feature of this proposal is our ability to leverage the considerable investments in electronic clinical information systems made by our member health plans to dramatically improve the scope, efficiency, and speed of data collection for clinical and health

services research. At the end of the support period, we will have established an informatics platform to support research that will be among the most powerful worldwide in its scope and applicability to clinical practice.

Dr. Ralston described the program objective to expand the research capacity of the HMO Research Network across the entire network of health systems. The network deliverables focus on providing research opportunities and increasing research interest among practitioners, project planning tools to streamline the budget and IRB review processes, creating best practices for distributed data models.

5.9 Critical Care Decisions: "Re-Engineering Clinical Research in Critical Care" - LDS Hospital, Principal Investigator: Alan H. Morris, M.D.

Aim #1:	*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*
Aim #2:	*Establish a new ICU clinical investigative strategy with currently operational integrated electronic tools (Utah Clinical Trial Toolbox) that can link different clinical research networks*
Aim #3:	*Enable investigators to uniformly implement and distribute knowledge-based ICU care and to address ICU clinical problems that have defied resolution with traditional clinical investigation approaches*
Aim #4:	*Standardize bedside decision support by the development of two frameworks for knowledge engineering and clinical decision support*

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. The use of explicit detailed computerized bedside protocols will increase the probability of finding differences between experimental groups. This new strategy will enable investigators to uniformly implement and distribute knowledge-based ICU care and to address ICU clinical problems that have defied resolution with traditional clinical investigation approaches.

We will engage 24 clinical sites in 4 study activities. Backup sites are readily available to change their participation and replace any sites incapable of discharging their obligations. Sites include academic, community, pediatric, adult (including geriatric), US and Canadian hospitals. Some sites are deeply invested in research and electronic infrastructure and others are exclusively clinical care sites with almost no such investment. This large number of diverse site has been expressly chosen to provide a highly credible test of feasibility. The diverse sites will provide a fund of participating investigators and hospitals ready to move directly to a large randomized clinical trial with linked research networks.

Investigators will participate in one or more of 4 activities. (1)- all investigators will contribute to the general work that includes planning and development of the proposed protocol and network linking strategies, organizational elements, monthly conference calls and twice yearly meetings in Salt Lake City. They will conduct literature research, writing, evaluate documents, and develop strategies to link the pediatric PALISI and the adult NIH/NHLBI ARDS Networks; (2)-eight selected sites will refine and establish safety of a common bedside computerized blood glucose protocol for adult and pediatric ICU patients; (3)- seven other selected sites will subsequently implement and use at the bedside these safe refined protocols for patient care; and, finally, (4)- three other selected sites will implement and use computerized Clinical Coordinator tools to aid conduct of clinical studies already under way and independently funded. Three different feasibility tests of the common electronic tools (refinement

of bedside protocol, use of bedside protocol in patient care, and use of the Clinical Coordinator program) for multiple purposes in disparate clinical settings should provide a credible and definitive evaluation of the feasibility of our proposed approach. We believe the likelihood of success is high and that this feasibility work and the large number of participants will prepare us to move directly to link research networks and introduce efficient ICU clinical trials on a large scale.

Dr. Morris described the program to standardize bedside decision support by the development of two frameworks for knowledge engineering and clinical decision support. This ICU based project uses established clinical trial instruments that include the following tools: forms developed by a computerized CRF builder, bedside data entry and decision support, CRC administrative support and central monitoring support.

5.10 ePCRN: "The electronic Primary Care Research Network (ePCRN)" - University of Minnesota, Principal Investigator: Kevin Peterson MD

Aim #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.*
Aim #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.*
Aim #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.*

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.

The principal aim of this proposal is to enable the development of an electronic infrastructure that facilitates the recruitment of subjects and the performance of RCTs in primary care practices anywhere in the United States, and that promotes the rapid integration of new research findings into primary care. This infrastructure is introduced into practice-based research networks of primary care physicians through the Federation of Practice-Based Research Networks (FPBRN). Consisting of over 6,500 physicians performing research in over 2,700 primary care practices, the FPBRN serves a patient population of approximately 16 million people. This new electronic infrastructure will be developed on the new OGSA platform for very high speed network communication called Internet-2 (or the Grid). Exciting possibilities for this technology include the potential for patient eligibility searches across wide geographic areas, real-time video conferencing, remote instrumentation, and high speed parallel processing. The development of a high speed electronic research network on open source Internet-2 functionality would form the foundation for a revolution in clinical research and in primary care in the United States.

This proposal is being accompanied by a complimentary $3.5 million proposal to the Medical Research Council (MRC) in the United Kingdom for development of an electronic Primary Care

Research Grid (ePCRG) in response to their eScience initiative. However, the MRC and NIH proposals are not contingent upon each other. A third proposal will be sent later this year to Europe under Framework 6. Such an international partnership allows substantial leverage in programming interfaces, standardization, and advanced infrastructure development for additional support of RCTs.

The development of the proposed electronic Primary Care Research Network (ePCRN) platform would provide the ability to perform large national collaborative studies throughout the US, improve efficiency, reduce costs for individual trials, provide easier access for data retrieval and analysis, and involve primary care in recruitment, performance, and translation of findings into practice. The substantially enhanced capacity of Internet-2 for data transfer, training, and analysis would promote the development of exciting new research applications including remote instrumentation and real-time video-conferencing, and will provide a vast resource for the future on which to expand and enrich the clinical research enterprise.

Dr. Peterson described the ePCRN translation objective to establish a clinic-based registry in primary care with established import and export standards as well as establishment of standardized dataset CCR (ASTM) versus CDA (HL7) that promotes clinical information exchange. To date, ten sites in Minnesota have been selected and ninety additional sites will be determined after the initial RCT. A registry is in development, though agreement between standard development organizations must be fostered. The technical objective is to port the combined solution to open source Internet-2 components that will allow additional functionality.

5.11 COG: "Developing a Collaborative Effort between the Pediatric Blood and Marrow Transplant Consortium (PBMTC) and the Children's Oncology Group (COG)" - The Children's Oncology Group (COG), Principal Investigator: Gregory H. Reaman, M.D

Aim #1:	*To expand COG's clinical trials infrastructure to enable an inter-operable clinical research network in pediatric BMT in conjunction with PBMTC.*
Aim #2:	*To evaluate the performance of the infrastructure and inter-network informatics applications in actual inter-group clinical trials.*
Aim #3:	*To develop standardized informatics tools that will allow for optimal data sharing of clinical research data from clinical trials between the COGIPBMTC and other networks.*
Aim #4:	*To optimize the PBMTCICOG clinical trials network structure as a model for performance of trials on rare and orphan disorders.*

The broad, long-term objective is to develop a collaborative effort between two clinical trial 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.

The project design takes advantage of the experience and expertise of the COG staff to train a small team, including a project manager, study coordinator and statisticians to support the development of PBMTC studies, and to expand the scope of the existing COG electronic data entry and database management systems to encompass the PBMTC, using flexible, user-friendly tools to accommodate their new requirements for study conduct. The strength of this approach will be evaluated by conducting three demonstration studies; the first a COG coordinated inter-group study. The remaining two will be PBMTC initiated, the first for treatment of idiopathic pneumonia syndrome, a rare complication of blood and marrow transplant, and the second a study of donor-related marrow transplant across several COG disease protocols. In addition to developing standardized informatics tools that can be used by both COG and PBMTC, we will explore collaborating with other BMT-related networks to share data from clinical trials.

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 integrating and expanding clinical research networks broadens the kinds of research questions that can be addressed and enhances 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 demonstrate that this goal can be achieved. This project will also confirm the robustness and flexibility of the tools and the systems developed by COG. At the end of the project, PBMTC will be able to continue conducting their studies with the same success using the infrastructure developed during the project.

Mr. Roy described the aims of the COG and PBMTC Joint project as the expansion of COG clinical trial infrastructure to enable an inter-operable network in pediatric BMT and PBMTC, eventually conducting inter-group trials. The enhanced remote data entry system is comprised of four main components; study manager system, remote data entry system, study report system, and scheduling system to allow flexibility, accuracy, efficiency.

5.12 RIOS Net: "Research Involving Outpatient Settings Network (RIOS Net) and Underrepresented Populations" - University of New Mexico, Principal Investigator: Robert L. Williams, M.D.

Aim #1:	*Increase the scope of network activities to include new scientific questions, disciplines, and/or tools and approaches;*
Aim #2:	*Increase participation, including appropriate training, within the network to include new sites, new patient populations and/or new investigators;*
Aim #3:	*Facilitate the communication and cooperation of RIOS Net with one or more additional networks*
Aim #4:	*Expand the RIOS Net information technology infrastructure and linkage capability*

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) conduct research in settings that lead to better translation of research into practice.

Fifteen specific objectives are proposed with associated milestones. These objectives include the expansion of network membership, the creation of an infrastructure to fast-track the research process in the network, the creation of enhanced capability for translational research, expanded training of researchers, enhanced capacity for community participation in research, the formation and testing of linkages to other clinical research networks, and the enhancement of network Information systems.

Dr. Williams highlighted the RIOS Net primary care practice-based research network of clinicians which serves the Southwest's low-income, medically underserved and culturally diverse communities. The program focus is on translating research findings into medical practice; enhancing clinical trials research infrastructure and involvement of community clinical practices with research. To increase the participation of providers and communities the program has hired "detailers" to assist site in the process of incorporating research involvement in their clinical practice.

6.0 Formation of Thematic Clusters / Working Groups

The group discussed the formation of working groups in order to (i) define how each group will be structured; (ii) outline goals, and (iii) draft plans for each group.

Investigators who wish to be a member of a group should submit their name to the University of Pennsylvania. (Contact dmccall@cceb.upenn.edu) The following Groups and Chairpersons were identified:

6.1 Clinical Research Network Development Strategies (Chair: Kevin Patterson)

Objectives:

- Primary care research network development and involvement
  - Feedback, EBM, CME, Payment, Time (%), Bottom up/top down participation
- Increasing involvement of community settings, particularly of diverse communities
  - Community involvement in AIDS research, Community Boards
- Opportunistic identification/case ascertainment
- Qualification and governance of individual physicians
  - Training and certification of a practice site, Security, HIPPA, IRB training/consent issues, NCRA qualification
- Recruitment and retention
  - Clinicians, Sites, Networks
- Site selection/evaluation
  - Minimum resources, capability (population, performance), past performance, sustainability of infrastructure, network partnership, specific study needs/interest

Topics to be explored by group:

- Primary care research network development and involvement, including retention of these referral centers via feedback and incentives.
- Increasing the involvement of community settings and reducing barriers to participation.
- Qualification and governance of individual physicians.
- Recruitment and retention of individual physicians.
- Site as customer - customer management/satisfaction.
- Site selection/evaluation and approaches to improving this process.
- Web site deployment of communication and productivity tool suites including email, conferencing, and document sharing.

6.2 Human Subject Protection and Regulatory Strategies (Chair: Carol Dukes-Hamilton)

Objectives:

- Advocate for Sensible Regulation
- Share Tools, Develop Tools for Common Use
- Research Develop Data Regarding Regulatory and HSP Effectiveness
- Roadmap group project
  - Develop survey instrument to administer to clinical investigators AND clinical study coordinators, attitudes and experiences with IRB, HIPAA, human subject protection processes, develop protocol
- Repository/library of approved “short forms” in numerous languages
  - Role for NIH as central/leadership/access
- Dictionary of definitions
  - Commonly used words/phrases, linking standardized lay-language with scientific definitions

Topics to be explored by group:

- Facilitating use of central IRB by getting stakeholders and others interested in a ‘think tank’ symposium and high level planning.
- Strategies for involving English as Second Language (ESL) participants.

- Development of HMO research network with coordinated IRBs

6.3 Interoperability and Developmental Strategies (Co-Chairmen: James Kahn and Stuart Speedie)

Objectives:

- Explore the menus for standards with particular attention to consolidation of standards important for clinical research
- Develop a menu of standard setting activities that we can influence relating to clinical research. Examples include: Commission on Certification on Health Information Technology; HL7; ASTM, etc.
- Influence interoperability including architecture, interface and support
- Influence models as mechanisms for sharing rather than the end products
- Work as a group to promote the success of individual projects

Topics to be explored by group:

- Provide a menu of desired and valuable standards to consider.
- Explore who is using standards and how these standards are being used.
- Identify leaders for standards development and implementation.
- Explore the interaction of groups developing and implementing standards.
- Standard definitions may be too granular a resolution; activity may need to provide standard frameworks and clarity to frameworks and structures.

6.4 Education and Human Performance Strategies (Chair: Alan Morris)

Objectives:

- Evaluate models and approaches to Human Behavior Modification including adequately explicit point-of-care computerized protocols
- Strategies and methods for training collaborators and other study personnel

Topics to be explored by group:

- Strategies and methods for training collaborators and other study personnel.
- Developing community relations.
- Raising the national 'research IQ'.

7.0 Administrative Issues

7.1 Contract Logistics and Deliverables

Lisa T O'Neill provided the following contract related information:

- A contract is different than a grant and requires monthly interactions between business offices and the institute in order to ensure timely submission of financial reports and invoices. A summary sheet of deliverables was provided by Lisa for Investigators. Each Investigator should provide this sheet to his or her Business Office.
- Financial reports due on a quarterly basis with the first due 31.JAN.05.
- Subcontracting plan requirements; start date 30.SEP.04.
- Due every 30.APR and 30.OCT, a 295 form annual report.
- 10.JAN.05 quarterly progress report – what has been accomplished to date, milestone revision if applicable, IT plans – should be submitted soon.
- Monitoring plans should be submitted by DEC.04, please see above discussion and NHLBI template.

8.0 Action Items

ACTION ITEM	RESPONSIBLE PARTY
Further Define Working Groups and Establish Memberships	Investigators communicating their materials to University of Pennsylvania for compilation and distribution
Attend to Contract Deliverables	Investigators
Submit Monitoring Plans to NHLBI	Investigators
Decision Regarding Web Portal Contract	NHLBI
Investigate Web-Based Communication, Productivity, & Collaboration Tools	University of Pennsylvania

The designated University of Pennsylvania contact for direct follow-up related to these meeting minutes is Ms. Dawn McCall (**dmccall@cceb.upenn.edu**). Please copy correspondence via email to Ms. Denise Cifelli (**dcifelli@cceb.upenn.edu**).