

**NIH ROADMAP
CLINICAL RESEARCH NETWORKS & NECTAR**

MEETING SUMMARY

**BUILDING COLLABORATION FOR
CLINICAL RESEARCH NETWORKS**

**RE-ENGINEERING THE CLINICAL RESEARCH ENTERPRISE
6TH STEERING COMMITTEE MEETING
MAY 9 & 10, 2007
*BETHESDA, MD***

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Wednesday, May 9, 2007 (Day 1)

Welcome and Introduction

Dr. Jody Sachs and meeting Co-Chairs, Drs. Lee Green, Kevin Peterson and Robert Williams, provided a brief welcome and introduction to the Sixth Steering Committee Meeting of Roadmap Clinical Research Investigators.

Barbara Alving, M.D.

Director National Center for Research Resources (NCRR), National Institutes of Health (NIH)

Dr. Alving began her comments by noting that NCRR will play a role in assisting the Roadmap programs in connecting with other NCRR activities. She encouraged the group to pose questions to NCRR that may facilitate improvement. She informed them of several other NIH initiatives (i.e. IDEA program and the Lariat Project) and encouraged Roadmap members to not only connect with each other, but to connect with these programs using development tools and collaboration styles. In addition to promoting collaboration within and across different programs, she emphasized the importance of investigator publications and communications to highlight the activities and achievements of the Roadmap program.

Anthony Hayward, M.D., Ph.D.

Director Division for Clinical Research Resources National Center for Research Resources (NCRR), National Institutes of Health (NIH)

Dr. Hayward provided a brief history of the connection between the National Center for Research Resources (NCRR) and clinical care networks. NCRR first expressed interest in clinical research networks in 2000 upon involvement with the Cystic Fibrosis Foundation and the Rare Diseases Clinical Research Network. Their interest in networks is fueled by the potential to recruit large numbers of patients that allows clinical research to be done more efficiently. This efficiency is created by avoiding duplication that otherwise goes on whereby either control data or lists of patients with every clinical trial is reinvented. He recommended that the group use the meeting to think about better ways of developing new collaborations and how to identify partners for these collaborations, how to adapt to the changing environment.

Organizational Science: Theoretical and Practical Methods for Promoting Collaboration among Clinical Research Networks – Arnold Kaluzny, Ph.D.

Professor Emeritus of Health Policy and Administration, School of Public Health, and Senior Fellow, Cecil G. Sheps Center for Health Services Research, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Dr. Kaluzny began by pointing out that the Roadmap program with its emphasis on re-engineering the clinical research enterprise requires a fundamental understanding of collaborative concepts and methods. His presentation covered key elements of effective collaboration and detailed various aspects such as distinguishing characteristics, challenges and methods for promoting collaboration. In addition he discussed the National Cancer Institute (NCI) Community Clinical Oncology Program (CCOP), an example of a successful program which provides lessons that relate to the clinical networks in the Roadmap program.

Clinical networks (often referred to as alliances/partnerships) are defined as a loosely coupled arrangement among existing organizations designed to achieve some long term strategic purpose that is not possible by any single organization. It is likely that their importance will increase as research activities continue to occur across, rather than within boundaries defined by formal ownership of one organization. As this occur, managers, clinicians and researchers will have to understand, more importantly, learn how to work with partners rather than subordinates.

Five Characteristics of Effective Network Collaborations (Kanter, 1989)

1. **Long term investment.**
2. **Networks are interdependent.** Mutual benefit should exist.
3. **Integration.** The whole must be greater than the sum of the parts.
4. **Members must be informed.** Middle management must be included in and committed to the process.
5. **Programs must be institutionalized.** In order to have an impact, networks need to become part of the fabric of the operations of an organization or a community.

Distinguishing Characteristics

1. **Distinctive process:** Networks don't emerge as fully developed entities but are formed through a series of stages (emergence, transition, maturity and crossroads). Different factors affect the major challenges that an alliance faces at the different stages.
2. **Commitment:** Effort, commitment, and enthusiasm are required from both sides if either is to realize the hoped-for benefits.
3. **Factors affecting success and failure.** Behavioral/system characteristics, e.g., trust, explicit operating rules, mutually understood expectations.

Managerial Challenges:

- **Different cultures.** Individuals from different environments (industry and academia) have different expectations. Different time frames can become problematic.
- **Realistic expectations.** Organizations must understand the cost of doing the work and generate realistic expectations.
- **Maintaining commitment over time.** Due to high turnover in organizations, constant re-socialization/orientation is required. Level of original commitment and knowledge does not necessarily remain due to turn-over.
- **Unfriendly incentive structures.** Within the academic community, single-authored publication is the currency. The pay-for-performance delivery system exists in this environment.
- **Uneasy tradeoff.** "Corporate need" for answers vs. "societal need" for understanding. e.g., proprietary vs. data sharing.
- **Mutually accepted performance measures.** Evaluation of programs/networks requires a metric for performance measures. "If you can't measure it, you can't manage it".
- **Sustainability.** Attracting/retaining new/young investigators.

Methods and Management Tools for Promoting Collaboration

- 1) **The balanced scorecard** is a management tool developed in industry which provides a comprehensive framework and focuses on basic dimensions which characterize the overall operations of the enterprise; internal business process, innovation and learning, customer and financial. (Kaplan and Norton, 2006) There is an increasing interest in the adaptation and use in a variety of health service organizations.
- 2) **Quality improvement methodologies.** Continuous quality improvement is well established within the health services community. It provides tools for monitoring the flow of activities as well as involves the relevant actors to continually improve the operations of the organization.

Examples of organizational networks within the health services and the clinical research community

- 1) **NCI, Cancer Research Network (CRN)**
- 2) **AHRQ Partnerships-Council of Partners/IDSRN**
- 3) **NCI, Early Detection Research Network (EDRN)**
- 4) **NCI, The Community Clinical Oncology Program (CCOP)**

The CCOP is a network/partnership involving the National Cancer Institute, selected cancers centers and cooperative groups and local hospitals and physicians whose mission is to bring state-of-the-art cancer care, prevention, and treatment to local communities by involving community physicians and their patients in NCI- approved trials. The objectives are to conduct treatment and cancer control trials in communities, improve community practice patterns, and diffuse state-of-the-art cancer care to these local communities. The CCOP program has several lessons learned that would be applicable to collaborations and activities of Roadmap.

Lessons from CCOP

- **Importance of personnel.** Nurses are critical to this program. They work within and between organizations in the community, and provide an important link into the cooperative groups and participating cancer centers.
- **Management selection of people.** Getting the right people involved is important in terms of creating networks.
- **Shared vision.** There are incentives beyond monetary gains. Recognize the human element and empower people to participate in a meaningful way.
- **Theory of small wins.** Involve individuals and communities in activities where they can succeed instead of establishing overarching goals. This provides visible accomplishments, encourages others and reduces resistance to future efforts.
- **“Single-loop and double-loop learning”.** Make sure that support people fully understand what the program is about.
- **Notion of trust in negotiation.** Individuals have to be committed to the idea and the time it takes to implement and institutionalize the idea.

Lessons for Collaboration

- Getting the right people involved is a central element.
- Manage the process through stages while being sensitive to the various stages and factors affecting the network.
- Maintain a long-run perspective.
- Involve meaningful and relevant activities such that all participants benefit.
- Provide periodic opportunities to reflect as a group.

Following his presentation, Dr. Kaluzny answered questions about the application of management concepts/methods developed within the business community to the clinical research community. He stated that within service delivery organizations unlike many components of the scientific community, there is more receptivity to using management methods like the balance scorecard and quality improvement. However, as the scientific community competes for increasingly scarce funds it is likely that greater attention will be given to the adaptation and application of management methods to enhance the research enterprise. As is often said, “The opportunities are at the intersection.”

Some Suggested Readings

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Promoting Collaboration in Clinical Research Industry-Based Collaboration in Clinical Research – Clive Meanwell, M.D.

Chairman and CEO of the Medicines Company.

Dr. Meanwell's presentation focused on the challenges of conducting effective and efficient clinical trials as seen from the perspective of the pharmaceutical industry. He highlighted the need for collaborative activities conducted towards a substantial and compelling shared goal and mission, with clarity of roles and responsibilities in an atmosphere of professional warmth and mutual supportiveness.

Dr. Meanwell discussed a number of different industry trials and the various issues and complexities associated with protocol development, planning and conducting clinical trials.

- **Trials are complex human endeavors** sometimes taking years to complete. As with any such project, professional planning, consideration of the inevitable trade-offs between time, costs, specifications and quality is an essential first task. Recent data show that inadequate planning is the root cause of delay in 25 percent of delayed projects and otherwise implicated in weak performance in about 40 percent of projects.
- **Front loading** (completion of set-up tasks prior to enrolling patients) is a critical capability. Set up tasks include comprehensive protocol review, data capture system testing and deployment, data base management tools, study tabular outputs, and adequate training of study staff. Too many studies begin recruitment before completion of these and other set-up tasks.
- **Study contract negotiation and institutional approval** may turn out to be significant sources of delay. It is essential that all parties have sufficient qualified resources for this aspect of study management
- **Recruitment objectives are generally over-ambitious**, particularly at the beginning of a study. Some data show that seventy four percent of Phase III study sites are below recruitment targets.
- **Protocol complexity** – a temptation driven by the desire to study patients comprehensively - drives case report form (CRF) complexity. These, in turn, drive observational, operational, data

management and analysis costs and time up – and often drive research quality down. The study team must pay rigorous attention to weed out superfluous questions, procedures, observations, and data fields that do not add significant value to the achievement of the study's main objective.

The pharmaceutical industry is facing a crisis of global complexity in many aspects of its business mode. During the last 10 years, new structures and processes have improved industrial R&D performance, but not enough to yield sufficient innovative products or satisfy investors. Specifically for clinical trials, a perceived mounting bureaucracy of regulation, increasing requirements for early comprehensive safety data, the obvious need for health economic data and a desire to maximize product launch yield worldwide have increased pressure on performance. Collaborative, authentic alignment of the beliefs, attitudes and behaviors of industrial and academic investigators remains our greatest hope for further improvement.

Clinician-based Involvement in Clinical Research: Primary Care Practice-based Research Networks (PBRNs) – David C. Lanier, M.D.

Dr. Lanier began his presentation with a definition of primary care practice-based research (PBRN). The Agency for Healthcare Research and Quality (AHRQ) defines primary care practice-based research as a group of ambulatory practices devoted principally to the primary care of patients, affiliated with each other in order to investigate questions related to community-based practice and to improve the quality of primary care. AHRQ began its support of PBRNs in 2000. In 1994, 28 primary care practice-based research networks were identified in the United States while there are now 177 PBRNs located across the United States and Puerto Rico. There is a distinction from other networks, in that PBRNs began as grassroots organizations in which clinicians and academicians in health centers or large hospitals came together and decided that the information they were learning from trials that were done specifically in academic and community settings, possibly lacked external validity to the practice settings in which they work.

Dr. Lanier discussed the capacity of practice-based research networks as having the following characteristics:

- Networks are reusable mechanisms for investigating care delivered in small community practices.
- Provide insight into mainstream care delivered to minority and underserved population.
- Longitudinal data collection provides an excellent place to study care over time.
- Direct clinical involvement and engagement in research design and interpretation of the data.

Examples of studies in PBRN setting

- Observational Study of Clinical-Research: Prevalence of night sweats in primary care patients.[Mold et al J of Fam Prac. 2002 May; 51 (5): 457-8].
- Protocol-Driven Clinical Research: NICHD sponsored a \$1.36 million pilot as part of feasibility for the National Children's Study to look at children over 20 years and the environmental influences on their growth and development.
- Translational/ QI Related Research: Interventional controlled study on smoking cessation.

Major issues identified with PBRNs

- **Ongoing infrastructure support.** There are minimal requirements for the sustainability of the network, including salary support for the director and the staff, and resources to develop grant proposals. There is a need for ongoing efforts to recruit and retain clinicians and maintenance and upgrades of network's information technology capacity.
- Less than 5 percent of affiliated organizations provide direct support to the PBRNs for work done, and about 50 percent provide some form of indirect support, which comes in the form of dedicated time for the director and staff. Funders often question the inclusion of compensation or reimbursement of clinicians or practices in budget request. In most cases clinicians are not reimbursed for their participation when the patient care flow is interrupted by a study. Should

physicians be reimbursed for the time that they spend performing in the research capacity instead of his or her primary responsibility during a patient visit?

- **Data gathering and aggregation.** The early network studies were done as card studies. With this approach, there were concerns about data quality and potential loss of data. In 2003 AHRQ developed an extranet site that included secure Internet-based portals for data collection for multiple geographically distant sites. AHRQ has supported pilot work with the use of Personal Data Assistants (PDAs), laptops and tablets for collecting data.
- **Traditional Research vs. Quality Improvement (QI) Effort.** How do we change processes within practices such that formidable results and outcomes are achieved? This is a new, emerging field which lacks rigorous methods for conducting or evaluating this type of effort. It also faces challenges in study sections where the typical study section member has trouble comparing Quality Improvement (QI) related studies to more traditional research.
- **Multiple IRB Reviews.** When networks are spread out over multiple states, there are national networks that fall under different federal-wide assurances. For an individual study, approval may have to be obtained from multiple IRBs. Practices have found this process to be cumbersome, sometimes resulting in elimination from studies. There are ongoing efforts with the Office of Human Research Protections to establish a central IRB.

At the end of Dr. Lanier's presentation, he held a question and answer session addressing questions related to the value of PBRNs to clinical practices and their future collaborations. Dr. Lanier indicates that the reasons for participation in PBRN go beyond altruism; physicians are interested in networks and projects that relate to improvement of the quality of care.

Community-Based Participatory Research and Collaboration Building: The Detroit Community-Academic Urban Research Center Experience – Wilma Brakefield-Caldwell, BSN and Robert McGranaghan, MPH

Mr. McGranaghan commenced by defining Community-Based Participatory Research (CBPR) as an approach to research that equitably involves academic, practice, and community partners in all phases of research. It is important to note that there is a distinction between community-based participation research and community-placed research. The former gives the community an active role in the actual research planning and development.

The following CBPR principles serve as a blueprint for how collaboration is done. There is a board of community and academic partners that mandates that the research being conducted adheres to the following key principles.

- Recognize the community as a unit of identity. Communities can be defined geographically, sociocultural, ideological, or some combination of all.
- Begin with and build on strengths and resources of the community.
- Facilitate collaborative, equitable partnership in all phases of the research, involving an empowering and power sharing process.
- Promote an approach where both sides of the partnership are learning. Promotes co-learning and capacity building among partners involved.
- Integrate and create a balance between knowledge generation and action for mutual benefit of all partners.
- Place emphasis on local relevance of public health and social problems and ecological approaches that address the multiple determinants of disease and well-being.
- "Community-based" versus "community-placed." Community-placed research takes place in the community while community-based research incorporates a partnership approach.
- Involve system development through a cyclical and iterative process.

- Disseminate findings to all partners and involves all partners in the dissemination process.
- Be long-term process and commitment oriented.

Mr. McGranaghan then spoke about The Urban Research Center (URC) that was established in 1995 with core funding from the Centers for Disease Control and Prevention through their Urban Research Centers Initiative. The center is based at the School of Public Health with Barbara Israel serving as the director and principle investigator. The core funding helped to establish the center and an initial demonstration project which gave the leverage to seek additional funding for other projects to address urban health problems. The mission of the URC is broad and overarching, addressing the social and physical-environmental determinants of health to reduce health disparities. Under this broad framework, projects that focus on a number of issues have been completed.

Currently, there are eight community-based organizations, the University of Michigan Schools of Public Health, Social Work, and Nursing, Henry Ford Health System, the main integrated health system in southeast Michigan, and the Health Department that has a partnership with the URC.

Since it's inception in 1995, there have been approximately 20 projects bringing in over 30 million dollars in federal, state, and foundation funding to conduct a variety of different projects focusing on areas such as diabetes management and prevention; asthma, cardiovascular disease, specifically looking at the social and physical environment and how it affects cardiovascular disease; access to health care and quality of care; domestic violence prevention. More recently, in the policy arena they have been trying to assist neighborhoods and communities in capacity building, while influencing policy changes to improve the quality of life in their neighborhoods.

Wilma Brakefield-Caldwell, B.S.N., Detroit Community-Academic Urban Research Center

Ms. Brakefield-Caldwell began her presentation with a description of the Community Action Against Asthma (CAAA), one of the URC's major projects.

The CAAA project involves a household and neighborhood community level intervention which studies environmental triggers on asthma and involves 300 families from areas around the URC. CAAA has an extensive data collection modality which includes annual surveys for parents and children, a household dust sampling and household environmental checklist, and seasonal assessment performed on a daily basis during one two-week period in 11 consecutive seasons.

The community members and the steering committee (comprised of the community, academic partners and affiliates with the Detroit Research Center) played an active role in the planning, development, and operational phases of the project. Their contributions included development and validation of survey instruments, protocol development, subject recruitment and retention strategies, training survey interviewers interpreting the results and serving as co-authors of the articles. The community also served to identify appropriate and inappropriate ways of conducting research in their community by identifying invasive questions and approaches such that the community would not feel that research methods being used were intrusive.

Ms. Brakefield-Caldwell concluded by noting that the involvement and presence of the community members in this project was critical in that they served as a voice for the community at large.

Rare Diseases Clinical Research Network (RDCRN): A Network of Networks - Elaine Collier, M.D

Dr. Collier focused her presentation on the Rare Disease Clinical Research Network (RDCRN) to exemplify the work of government-based collaboration. Approximately 25 million people in the US are affected by approximately 6,000 rare diseases such as bone marrow failures or hematologic diseases, thrombolytic diseases, rare genetic steroid diseases that cause ambiguous genitalia and urea cycle disorders, multiple differing types of vasculitis, inborn errors with genetic defects, Prader Willie Syndrome, and liver diseases.

To address this issue, the NIH established the RDCRN in 2003, originally consisting of four consortia and a data and technology coordinating center. This is a complex network in that each consortium focuses on a subset of diseases and consists of multiple investigators and sites therefore creating networks within a network. These consortia include both foreign and domestic sites.

Patient advocacy groups were involved in the process as well, as part of the original application for each consortium. The advocacy groups formed their own coalition and taught each other the mechanisms of grant funded research and how to be a support system for the people they serve.

A national standard approach was developed and incorporated from the perspective of the NIH. To facilitate this, the data center hired a medical informaticist knowledgeable about the terminologies, vocabularies, and informatics. Standardized approaches were developed using a variety of tools and instruments, such as the following examples:

- Use of Standardized Terminology and Vocabulary (i.e. SNOMED)
- Standards incorporated into protocols, data collection forms, database, adverse events reporting.
- Data Collection techniques such as Interactive Voice Recording for participant reporting and automated database population.
- Standardized Videotaping of Stereotypic Movements.

Dr. Collier noted the Rare Disease Clinical Research Network website:

<http://rarediseasesnetwork.epi.usf.edu/>, an interactive website that includes information for the public, caregivers, and scientists. This secure website allows web conferencing that enables investigators to see their unblinded data. Members have access to active studies and information about various consortia and diseases. There is also a contact registry, accessible via web, phone, or mail, developed and maintained by the data coordinating center. Here, interested individuals with rare diseases can register and obtain information about new studies and receive newsletters from each of the consortia that are focused on various diseases. This platform serves as a way to develop trust and a connection with the community. While not all information from the registrants is dispersed to investigators, some information is collected such that they can funnel the information that goes out. Some of the issues that are unique across the network are ethical issues related to genetic studies, informed consent issues, and the standardization of elements. This has promoted cohesion among each of the consortium.

Dr. Collier concluded her presentation by outlining the following lessons learned:

- Involvement of the patient advocacy group is critical and mandatory.
- The lack of experience in working in networks leads to competition versus cooperation.
- Flexibility is needed to allow for differences and emphasize commonalities.
- Expectations need to be managed due to various levels of expertise and experience in doing clinical research.
- Accommodation is necessary to address style differences in the diverse disease communities and groups.

In closing, Dr. Collier held a question and answer session, addressing issues related to access to information and computer literacy.

Identifying Current Organizational Problems in Promoting Clinical Research Collaboration: Investigator Case Study Presentations and Panel Experts Evaluation and Discussion

The case study presentations detailed issues and barriers in forming partnerships and collaborations. The investigators and panelists made salient points in response to case study presentations thus providing a vibrant discussion.

Case Study #1: Cultural Differences and Effective Collaboration: Two contrasting stories of collaborations involving minority communities in Seattle.

Dr. Eric Larson provided a description of two contrasting projects that provided insights into the different experiences of collaboration involving minority communities in Seattle, Washington.

The first of the two projects was the KAME Project which was a study on dementia and Alzheimer's disease set in the Japanese American community of King County, Washington. Initially there was reluctance when the investigators proposed the project. They expected there to be a natural reluctance from the community to being "counted" and singled out for enrollment in a research study aimed to determine prevalence, and ultimately incidence rates and risk factors for dementia and Alzheimer's disease. To address these issues, a community advisory board was formed consisting of clergy, community leaders, and social workers. Considerable time was spent detailing the project to the community prior to implementation, as well as involving members as staff to execute the project.

The second project focused on an organ transplantation program for persons suffering from end stage heart, kidney and liver diseases in the African American community which involved a reputable cardiac surgeon. This project involved a short planning phase and limited endorsement. In the end the project was abandoned.

Panel Discussion Comments:

- Community involvement in developing the design of a project and its conduction is primary. The success of a project and long-term engagement of the community for future projects is dependent on these steps.
- Joint development of hypotheses can be effective.
- It is important to find areas of synergy that represent perspectives of academicians and community members.
- Communities should recognize and be sensitive to issues and priorities that exist in their environment. Researchers should recognize this as a mechanism to build trust, and form relationships.
- "Helicopter studies" are a mistake. A network's longevity and future involvement in a community is a result of community benefit being provided.
- Bottom-up vs. top-down studies. Bottom-up studies are time consuming but less paternalistic, involving community engagement (buy-in or ownership). There are tradeoffs to the 2 different approaches in that bottom-up studies are more time consuming and costly while top-down studies can be done more efficiently. In multi-site studies, both approaches should be explored.
- Time commitment is both important and expensive and relies on volunteerism, particularly by community members.
- The intrinsic value of volunteerism in collaboration should not be discounted. This element adds value if you have the relationship with a community that enables or excites individuals to volunteer.
- Involving community members as staff people, interviewers, or out-reach workers serves to educate and create awareness and, lessen distrust which serves to increase study participation rates (i.e. survey response rates and focus group participation).
- Concepts of risk, benefit, randomization and other research vocabulary are difficult for communities to understand.

Case Study #2: Community reluctance to participate in clinical research activity

Dr. Robert Williams provided a brief description of a RIOS Net project. A set of 18 focus groups were conducted among people in the Hispanic, Native American, and immigrant communities around the state of New Mexico, to explore health services research or low-risk research and reasons for reluctance to participate in clinical research activities.

The focus groups excerpts cited the following issues as reasons for lack of participation:

- Lack of community benefit.
- One-directional process.
- Exposure to risks on the community and individual level not addressed or properly protected against in the research process.

Panel Discussion Comments:

- Patients misunderstand that normal health care delivery under competent providers and that participation in a research program which follows regulatory requirements are all fraught with potential risks and uncertainty. This is an important issue regarding perception of research and the link to trust.
- Behavior change is a major outcome variable.
- Community reluctance which may be based on misunderstanding should be promoted by informing individuals that research participation has benefits.
- Patient awareness and risk aversion is based on past experiences with research and researchers. Communities feel that there are unbalanced outcomes from research without a direct provision of benefit. Examples of this include 1) negative sentiments about the CDC and the Hantavirus outbreak in the Four Corners area that released negative publicity about the Navajo tribe and 2) studies regarding alcohol use emphasizing negative aspects of alcohol use in Native American communities.
- The nature of the research process does not have a built in process for applying results directly to the benefit of the people who are part of the community that participated.
- Individuals remember unfavorable experiences.
- Intervention, information, and referrals are seen as benefits to research participation.
- Commitment is necessary on the part of the investigators to work in the direction of partnering with individuals who can influence policy change to provide answers to health issues in communities once the research is complete.
- A community must make the decision to invest energy, time, and resources in projects.

Case Study #3: Academic Health Centers and Community Clinicians-barriers in forming Partnerships

Dr. Kevin Peterson described a Center for Disease Control (CDC) initiated study involving Practice Based Research Networks (PBRNs) of primary care clinicians and a clinical research organization (CRO) to evaluate clinical laboratory tests in the diagnosis and treatment of urinary tract infections. Due to the untimely passing of the original investigator, a senior investigator with experience in public health epidemiology from a contracted CRO was selected to lead the study. Several issues surfaced resulting in closure of the study.

Panel Discussion Comments:

- Burdens are imposed on practices during collaborations; there is an interruption in patient flow and practice patterns as a result of the study.

- The enterprise of doing research requires goodwill, trust, and enthusiasm for doing studies. Improved processes of care can provide benefit.
- Illustration of the tension between effectiveness and efficacy research: A CRO efficacy study concerned about internal validity is being implemented in a setting where clinicians are concerned about effectiveness. Different world views and views of research are coexisting.
- Practitioners must be provided with tools enabling them to capture necessary data while returning some benefit to them in the process. The absence of tools to aid practitioner can cause inefficiencies in medicine.
- The commercial CRO industry performs research in an efficient manner which is designed to minimize risk and return profit.
- Simple training program promotes practice engagement.
- Recognizing effective collaboration and averting unfavorable outcomes: It is necessary to implement rules to stop a trial based on unexpected early evidence of benefit or harm.
- Participating practices incur significant costs not covered during participation in research.
- Underestimation of costs in research can produce detrimental effects. Center Watch conducted a study, citing the number one reason people get out of research is because of money. Adequate funding is typically not provided to multi-site trials to cover all the costs.

Case Study #4: Role of Participants in Funding Research Study

Dr. Elaine Collier presented a case study about a not uncommon problem frequently encountered in rare diseases and the Rare Disease Network. The problem is the lack of interest in funding research in rare diseases at the industry level and at the payer level. The source of this case study is the article: "*Paying to Keep Your Drug Trial Alive*" by Amy Dockser Marcus, [*The Wall St. Journal, April 10, 2007*](#). **Note: The study cited in this case presentation was not conducted in the Rare Disease Network.**

The case focused on the financial struggles that occurred in a clinical trial testing a drug for treatment of a rare disease, amyotrophic lateral sclerosis (ALS). The physician investigator sent letters to the study participants informing them that the study may close as funding was not available to purchase the drug, and he requested funds from the participants to continue the study. Seeking funds directly from patients raises ethical and economic issues. Unusual fund-raising tactics underscore a great challenge in the world of rare diseases, where few treatment options may exist. Pharmaceutical makers see little financial benefit in studying drugs for rare diseases, so doctors and patients must find creative solutions to support the needed research of the disease.

Panel Discussion Comments:

- Though it is unknown whether there was IRB approval for this activity, it was noted that frequently IRB's have a very paternalistic attitude about their role in the protection of patients with rare disease.
- Failure to be cost-effective in how research is conducted has resulted in an increase in research activity being conducted outside of the United States.
- How does one justify spending substantial amounts of money on the rarest of diseases? An argument for funding rare diseases should be tailored along lines of the magnitude of the impact that such a study could have, in comparison to the amount of funds expended.
- A benefit of research is not just in discovering what worked, but also demonstrating what did not work. This can be very beneficial at the community level when relating the value of research.
- Risk aversion and risk sharing should be fully addressed at the organizational and IRB levels.
- Community over-sight is an important component in rare disease research. The NIH has community participation on the safety monitoring boards overseeing rare disease studies and requires that patient advocacy groups be involved in the development of study protocols.

The Sentinel Network – Jeffrey Shuren, M.D

Dr. Shuren began by introducing the concept of *The Sentinel Network*, and the basic premise surrounding its formation. Because healthcare practitioners and patients need up-to-date and accurate information about the risk/benefit profile of medical products to use them safely and effectively, the Food and Drug Administration (FDA) is establishing the *Sentinel Network* project. The goals for this project are to: 1) integrate, collect, analyze and disseminate medical product (including human drugs, biologics, and medical devices) safety information to health care practitioners and patients at the point-of-care; 2) reduce, through surveillance and observational study, morbidity and mortality from drugs, biologics, and devices in a much more timely and efficient manner; 3) leverage health information technology tools to facilitate the acquisition, analysis and communication of new risk information.

The Sentinel Network should be a coordinated public/private effort that would leverage, and build upon, existing data resources/programs in both the public and private sector. National and international standards adopted by the American Health Information Community (AHIC) should be used. Currently this project is underway in collaboration with several other federal agencies including the National Institutes of Health (NIH), Center for Disease Control (CDC), Agency for Healthcare Research and Quality (AHRQ), Centers for Medicare and Medicaid Services (CMS), Department of Defense (DOD), and the Department of Veterans Affairs (VA).

Dr. Shuren identified the following components that will comprise the *Sentinel Network*:

- Data Collection
 - Integrate clinical practice and post market safety surveillance
 - Use multiple data sources, e.g., EHRs, lab data, radiological studies, pharmacy records
- Risk Identification and Analysis
 - Develop and validate data mining tools
 - Reach agreement on methodologies
 - Establish integrated research networks
- Risk Communication
 - Leverage healthcare practitioner community expertise
 - Integrate new risk information into the workflow of clinical practice (e.g., decision support systems)

The FDA held a 2-day public meeting on March 7 -8, 2007, to discuss the envisioned *Sentinel Network*. They received public comments through April 5, 2007, and are currently drafting a white paper that will address the details of the functions of the network, and critical areas to focus on in private-public collaborations. These network functions include:

- Rapid identification of known or suspected risks
- Testing hypotheses and confirming signals
- Determining whether therapeutic products are appropriately used
- Identifying unsuspected risks

The future *Sentinel Network* will be a public-private partnership focused on existing efforts and not creating a brand new network, to make data results open and publicly accessible.

Dr. Shuren spoke of the opportunities envisioned with the *Sentinel Network* project, categorizing them in four areas:

1. **Enhanced Adverse Event Reporting** – Using the tools of Health Level 7 (HL7), the FDA is working with NIH and CDC to develop an electronic standard for AE reporting called the

Individual Case Safety Report. Use of electronic health records and data transmission standards that assist in identifying adverse events are being evaluated and user-friendly interface models for reporting adverse events are also being explored.

2. **Active Surveillance** – Different systems models for active surveillance are being evaluated for events that are drug-based, environmental setting-based or disease-based. Bioinformatics infrastructure for connecting and linking information from multiple systems and for data mining software will need to be validated for surveillance purposes.
3. **Streamlining Confirmatory Studies** – Developing larger standardized data sets through economies of scale to reduce the costs of conducting studies is also being considered. This will involve linking with a variety of institutions to share registry data and enhance epidemiologic study capability. Use of safety biomarkers is underway for post-market surveillance.
4. **Providing Incentives** – Shared interests and models for pooling of funding sources from private and public interests will be explored. Encouraging healthcare practitioner participation using the electronic health records will be an important element for adapting post-market surveillance activity.

At the end of Dr. Shuren's presentation, he held a question and answer session with the Roadmap Investigators, addressing questions related to the purpose and scope of the *Sentinel Network*. Questions regarding the use of pharmacogenomics, genetic data, electronic health records, large databases and health information sharing, information transparency, risk communication and protection of patient privacy were addressed.

Thursday, May 10, 2007 (Day 2)

Introduction

Anthony Hayward, M.D., Ph.D., Director Division for Clinical Research Resources National Center for Research Resources (NCRR), National Institutes of Health (NIH)

Dr. Hayward presented an overview of the Clinical and Translational Science Awards (CTSA) Program. He described the CTSA as a large and developing program that will expand into a nationwide consortium of 60 leading academic health centers by the year 2012. The mandate of the program is to strengthen the discipline of clinical research. He identified three guiding principles that distinguish the CTSA program from previous NCRR programs. 1) The program operates as a consortium; 2) There is an integration of training programs and the creation of degree courses leading to Ph.D's and Masters in clinical research; 3) informatics will play an important role in data sharing and in allowing more rapid access to information. The major focus is to speed the translation of treatments and interventions from bench to bedside and bedside out to the community. He noted that there has been a very positive commitment from the 12 awarded principal investigators, strengthened by the recognition that we are entering a new phase of clinical research in this country and the importance of succeeding in working together in sharing data and information.

Dr. Hayward also noted recent activities in the International Clinical Research Network realm and the wider range of countries that are organizing themselves to create effective and functional clinical research networks.

Dr. Hayward spoke of the lessons learned from NCRR's involvement in CTSA's and CRNs. He identified the importance of good and effective communication particularly on the level of direct personal contact and its benefit in cultivating collaborative relationships. Another lesson learned is the importance of transparency and making the program activities accessible to everyone. He noted that the CTSA steering committee meetings are made available through Adobe Connect, an interactive web conferencing communication system, and anyone who wants to can log on. Communications will not all be web based however, and annual in-person meetings will be held.

Dr. Hayward ended his talk by reminding the investigators that the most important outcome from their Roadmap work will be their publications.

Collaboration in Biomedical and Health Services Research – Joe V. Selby, M.D., M.P.H.

Dr. Selby began his presentation with an overview of the Health Maintenance Organization (HMO) Research Network structure, which he noted is a collaboration of 15 research centers, not just collaborations of the health plans. There are 15 million people receiving health care through the HMO Research Network. He described the network as collaborations of research centers with over 200 researchers (epidemiologists, health service researchers, economists) inside of the health plans, spread geographically across the United States. Many of the HMO research projects are conducted in partnership with academic institutions and large federally funded collaboratives such as the National Cancer Institute (NCI) Cancer Research Network, the Centers for Education and Research in Therapeutics (CERTS) funded by Agency for Healthcare Research and Quality (AHRQ), and the Vaccine Safety Data Link (VSD), funded by the Center for Disease Control (CDC).

Dr. Selby outlined the benefits that HMO-based research centers bring to research and he also outlined what HMO researchers need from their collaborators. The benefits include comprehensive electronic medical record (EMR) data on large defined populations, experienced researchers who work closely with

clinical and organizational leadership, standardized, validated data, and good relationships with the member populations. The HMO-based researchers need the expertise of clinical researchers, specialists in epidemiologic methodology, molecular biologists and geneticists, economists and anthropologists specialized in organizational change, and mentors for the younger trainees at the research centers.

Dr. Selby noted that the Kaiser Permanente organization works across the spectrum of research, which includes basic epidemiology, clinical trials, translation research and operations research and noted the similarities of their activities and the activities of the Clinical and Translational Science Award (CTSA) initiative – translation from bench to bedside to community practice. He detailed the Kaiser Permanente Research Program on Genes, Environment and Health (RPGEH), noting that this is an example of how Kaiser can engage with scientists in academic settings through the CTSA's. Its aim is to build a comprehensive genetic epidemiology resource of genetic and environmental influences on health. They are using clinical data from the EMR of 3.4 million members, participant survey data, and environmental exposure data from census data and other environmental mapping sources. They plan to collect DNA samples on 500,000 consenting adults. They have built 15 disease/trait registries that include survey data of demographics, education, personal and family health history, diet, physical activity, and other elements not always captured in an EMR. The program includes a biorepository of DNA specimens from consented members.

In closing, Dr. Selby gave some examples of Kaiser Effectiveness Research – an analysis of outcomes and utilization information showing variations in care and practice found within and across the HMO networks. He concluded his talk by emphasizing the keys to successful collaboration: looking for win/win situations that identify opportunities for research, building trust, and celebrating and building on successes achieved.

Case Study Results – Foundations, Best Practices, and Tools – Lee Green, M.D., Kevin Peterson, M.D., Robert Williams, M.D.

Dr. Green, Dr. Peterson, and Dr. Williams presented a summary of the themes that emerged from the case studies presented on Day 1, noting that the intent of using case studies was to gain insight and understanding from the experts on the most critical problems in building collaborations and the tools needed to move collaboration forward. With regard to network collaboration in industry and academia, many of the challenges they found are challenges common to other organizational networks.

Dr. Kevin Peterson remarked on particular challenges to collaboration presented in the Academic organization in such areas as:

- Promotion and tenure
- A balanced control versus the individual control of the principal investigator
- Working across disciplines as partners not subordinates
- Development of an explicit strategy of participation

Dr. Peterson noted that some of the common network collaboration challenges found within the academic environment included the following:

- Realistic time estimates
- Shared vision
- Management of participant selection and relationships
- Visible accomplishments – providing small wins

In summary, Dr. Peterson stated that investigators in the academic environment must develop a consensus rather than an individual direction. Also needed is sequential implementation of a specific

plan, aligned incentives, and prerequisite skills. He concluded by stating that a great deal of training is going to be important in the development of networking.

Dr. Lee Green focused on common themes relevant to a foundation for building successful collaborations with community clinicians, regardless of whether they are practice-based, hospital based, network-based, or academic-based. Common themes include:

- Strong relationship building requires considerable investment of time and energy. Relationships are partnerships built on flexible and equitable negotiation.
- Establish mutual reward.
- Avoid discontinuity in key research personnel.

Dr. Green spoke of people comprising the essential infrastructure of collaboration and the alignment of processes with value to organizations. He also spoke of related issues such as financial investment in the process, academic and clinical incentives, and sharing of information technology.

Dr. Robert Williams spoke about community collaboration and the need to consider the nature of the research being conducted in the community. He emphasized that the most important element of collaboration in the community is the need for mutual respect and trust between the partners. Community representatives need involvement in the research process, helping to define priorities, methods used in conducting the research, and assisting in the interpretation of the results. There needs to be bidirectional communication and investigator sensitivity to the culture and history of research in the community and to community-level risks, as well as fully informed community approval with compensation on both sides. Dr. Williams expanded on the point that communities must receive benefit from collaboration. Community benefit could take one of many forms, such as education about health topics, financial compensation or hiring of local community members to be part of the research team, training of health workers by someone in the community, or an intervention developed as a direct outcome of the research the community was involved in. This can lead to community health improvement rather than further description of health problems in the community.

Strategies for meeting the key elements for collaboration were outlined by Dr. Williams. The most important is living the key elements of collaboration as outlined above. Next is investing in the communication process such as having outreach workers skilled in the language of the community and taking into consideration the cost required to conduct the research. Flexibility in negotiating in good faith is required, and investing in the relationship. It is also important to plan for early successes so that the community begins to develop trust that you will deliver on what you say you will.

Dr. Williams concluded his presentation by stating that the principles of collaboration are not rocket science, but the implementation of these principles into clinical research networks is a bit like rocket science. The cost of expanding collaboration between networks and other parties needs to be addressed. In any collaboration, the stakeholders must see and receive benefits from the relationship and have a shared vision.

Clinical and Translational Science Award (CTSA) - New Collaborations

- Stephen Johnson, Ph.D., Columbia University
- J. Richard Landis, Ph.D., University of Pennsylvania
- Robert Harrington, M.D., Duke University
- Mary Durham, M.D., Oregon Health and Sciences University/Kaiser Permanente Center for Health Research

Funded by the National Institutes of Health (NIH)-National Center for Research Resources (NCRR), the [Clinical and Translational Science Awards](#) (CTSA) is a Consortium of 12 institutions bridging basic, clinical and translational research to bring effective strategies and treatments into medical practice more

rapidly. Four of the Roadmap Clinical Research Networks Investigators are involved in the CTSA consortium and each gave an overview of their CTSA program.

Dr. Stephen Johnson presented an overview of the CTSA program at Columbia University that involves social science research and how clinical research operates. Columbia is focused on community practice networks, in the suburban, rural, and urban areas. In the Roadmap initiative, the identified stakeholder population for understanding the social processes of clinical trials research is clinical coordinators and research nurses. The relationship of the research coordinators to the network administrators had emerged as an important communication pathway. CTSA is focused on the investigators and the collaborative resources that the investigators need to conduct clinical research. This includes resources in the realm of biostatistics, informatics, regulatory compliance, and ethics. With this, they are also looking at the barriers in each of these resource groups that impede collaboration.

Dr. Johnson's particular focus is on informatics. They are creating a stakeholder database of their systems users and available experts – an online profile that researchers can access for support. The information system they are constructing will have functions for search and matching. When an investigator identifies a need, the system will try to match the investigator with the resources or experts that can assist with the need. The goal is to start the collaboration and track it on line. The concept is based on a social engineering approach.

Columbia has no degree program where you can learn how to be a clinical researcher. Clinical research spans numerous programs and schools of the University. Re-engineering the educational programs to transition beyond discipline specific boundaries into collaboration to do translational research is enormously difficult.

Research readiness and the community practice networks are also an important aspect. Research readiness from an IT perspective is an assessment of how ready is a particular site to use IT for electronic medical records (EMR) for research. There is also clinical research readiness and the problem of different networks needing preparation and training in how to conduct clinical research.

Along with informatics and technology, Dr. Johnson identified social factors involved in developing collaboration technologies as an important area that other CTSA counterparts need to focus on, besides budget, standards and interfaces.

Dr. J. Richard Landis began his presentation of the CTSA program at the University of Pennsylvania by first giving a brief overview of how the work in the Penn's Roadmap program has influenced the work of the CTSA program. He noted that the first effort was an attempt to demonstrate to Penn Investigators that re-engineering materials can improve the quality of their clinical research. It is not a technology issue, but is really a cultural issue of trying to demonstrate that working in a standardized way could actually improve the quality of their research. Another challenge was to demonstrate to the University that the NIH is serious about clinical research engineering and that the "PI-centric business as usual" model cannot be sustained in the future. Dr. Landis stated that there is a tremendous fear among researchers that using standard methods and tools is somehow going to make things harder. The Penn Roadmap efforts attempted to demonstrate that by employing standards and infrastructure they are not creating barriers, but can actually enhance the conduct of the research. Penn is attempting to move beyond the "PI-centric" model toward an "enterprise-wide" model for clinical research informatics.

The PI for the University of Pennsylvania CTSA is Dr. Garrett Fitzgerald, who is also the Director of the Institute for Translational Medicine and Therapeutics at Penn. Dr. Fitzgerald recognized that a foundational challenge in translational research was the need to integrate data across the entire spectrum of data types and the methods utilized in that effort. He is particularly focused on the personalized medicine paradigm and the ability to link research data across the genotypic and phenotypic attributes, but also to be able to use data from the inpatient and outpatient contacts, labs, images, specimens, procedures, etc., and integrate those data elements from the various domains into an individual data record for analysis.

Dr. Landis cited as an example the cardiovascular risk assessment of the Cox-2 agents and the associated data integration challenges. He noted that a major problem is that many databases contain disease-specific data. In order to achieve the goal of personalized medicine, a disease-independent, comprehensive enterprise-wide data integration and analysis approach is required.

As part of the Penn CTSA, a Biomedical Informatics in Translation (BIIT) Center has been formed. The Center is proposing an informatics framework that has the following elements:

- A centralized IT and data architecture and research data facility. This will include standardized system security not only at the facility level but also at the data access level.
- Integrated biomedical and clinical research informatics toolkits to support the biostatistical and statistical genetics methods and applications, research computing, and integrated data analysis. This will enable data to be sharable and interoperable.
- Informatics highway with connectivity (i.e., IT plumbing) among data repositories.
- Data standards within and between Penn and Children's Hospital, facilitating clinical care and research enterprises to implement data interoperability, data integration, and data sharing.

Out of the re-engineering network of Roadmap, the Center for Clinical Research Informatics (CRI) was formed to develop and promote common tools, standards, and methods to enhance coordination and connectivity among the various groups, using the CTSA as a mantra to promote this.

The Penn CTSA BIIT vision is to integrate person-level data sharing between the clinical care enterprise and the clinical research enterprise. The Penn health care systems data must be accessible to the Penn clinical research enterprise in order to optimize the beneficial symbiosis of the two. Efforts are underway with industry (Oracle and IBM) to discuss the database architecture for these tools as well as the analytics.

Dr. Landis concluded his presentation by stating that the Roadmap re-engineering program has been an incubator that has permitted Penn Medicine to develop some of the critical and fundamental perspectives and technologies required for the future of CTSA. He specifically thanked NCRR for their vision and support.

Dr. Robert Harrington presented an overview of the Duke Translational Medicine Institute (DTMI), a CTSA department headed by Dr. Robert Kaliff. The span of the DTMI is from basic discovery, translation into proof of concept, to clinical research, translation and adoption to global health. Within the confines of an academic medical center and academic collaborations, they want to speed this process and reduce the time needed in which to accomplish their goal from 15-20 years to 10-12 years

Dr. Harrington outlined the concepts underlying the DTMI as they relate to the utilization of human resources such as getting R01-focused scientists to work in a project-oriented way, and the sharing of technology across large groups of people and investigators. He also outlined the following concept related questions: Will an early investment in human studies infrastructure lead to a better way to predict whether a research concept might be successful? Can we redefine clinical epidemiology by reclassifying diseases using molecular and imaging signatures? Can we develop an informatics infrastructure that aggregates, transports, and shares data to provide a capable electronic health record that leads to a repository that integrates research, clinical, administrative and financial data to enable disease state modeling? At the local level, is our expertise in health services research relevant to the Duke Health System? Can we actually demonstrate that we reduce death and disability in Durham County? Will doing research on research enable better research to be done?

Dr. Harrington presented a graphic of the organizational structure of DTMI, illustrating the three distinct institutes that now reside within DTMI: Duke Translational Research Institute, Duke Clinical Research Institute, and Duke Community Clinical Research. He outlined core resources that cut across the institutes. They include core laboratories, regulatory affairs, research ethics, nursing, biomedical

informatics and biostatistics, education and training, and pediatrics. To facilitate the notion of collaboration, translational research at Duke is organized around five thematic areas: 1) Cell processing and Cell Therapies, 2) Combinatorial Chemistry and Molecular Therapies, 3) Imaging, 4) Bio-repository for proteomics and genomics, 5) Vaccines. Encompassing all of these areas is Project Management and Bioinformatics, an organizational approach to educate basic scientists about project management and facilitate the movement in research from the silo approach to the project approach. Duke CTSA put out an RFP to the basic science community to produce a proposal that they wanted to accomplish with some seed money in the range of \$50 to \$100,000 per project. A basic scientist, a clinical scientist, and someone from the business school reviewed each proposal. Out of 65 applications received, 10 were funded because of the exceptional materials submitted in the proposals.

Dr. Harrington heads the Duke Clinical Research Institute (DCRI) of the DTMI and spoke of the contributions made by his division. It is the longest-standing institute in the DTMI, with over 900 staff and 200 faculty members. It houses many research networks and collaborates with a variety of people in academia, industry and around the globe, currently enrolling 555,000 patients in studies conducted in 64 countries. Dr. Harrington noted that the Roadmap project- Clinical Trials Network Best Practices has been utilized as a framework to help promote understanding of how networks can come together and accomplish their goals. The DCRI has a number of federally funded networks and networks supported by professional societies. There are also coordinating center networks and site networks such as the Cardiovascular Trials Group that Dr. Harrington previously headed as the core of the Duke Roadmap project. He also named a number of clinical registries housed within DCRI that have been made available to CTSA investigators. At the community based research level, a key construct is participation of residents in the planning and interpretation of research. Within the next 3 to 5 years, they hope to have an electronic health record in use throughout Durham County.

In concluding his presentation, Dr. Harrington spoke of the cyclic nature of advancing from discovery to clinical research, out to the community, and back again. He demonstrated this with a graphic slide entitled: "*The Cycle of Quality: Generating Evidence to Inform Policy*" that was recently published by his group in the journal, *Health Affairs*. Dr. Harrington noted that you have to think about the ways that you collaborate with discovery scientists, clinical investigators, and observational researchers, and with external parties such as industry, regulators, and other academic institutions.

Dr. Mary Durham began her presentation with a focus on the key organizations and their collaborative relationships established within the Oregon Health and Sciences University (OHSU) that led to the development of the CTSA and formation of the Oregon Clinical and Translational Research Institute (OCTRI). These key organizations include the OHSU academic schools, the Kaiser Permanente Center for Health Research, the OHSU and VA hospitals and clinics, and the Oregon community resources. Utilizing an EPIC-based clinical information system, OHSU in partnership with Kaiser Permanente, has been able to implement the use of electronic medical records as a beginning step in the process of integrating health care research and health care delivery. As Director of the Kaiser Permanente Center for Health Research, Dr. Durham spoke of her close work with Dr. Eric Orwall, the Principle Investigator for the OHSU CTSA and the partnerships formed in the OCTRI to advance translational research.

Dr. Durham outlined the following components of the OCTRI:

- Research support and operations utilizes project management, compliance functions and financial management to help investigators manage research projects.
- Clinical and translational research center, which is a new version of a GCRC for the out-patient research clinics.
- Educating non-basic science researchers about genetics and genomics and teaching basic scientists about population science and research
- Integrating biostatistics from the Center for Health Research and OHSU into a more common faculty to address projects and research problems that require their specific expertise.

- Translational technologies and creation of a biolibrary to catalog existing specimen data so that it can be shared with groups of investigators across the organization.
- Developing a biomedical informatics program to help OHSU and the community partners integrate their research databases thru a common platform.
- Community-based research through a robust program of practice-based research networks that are not only Kaiser Permanente providers, but also other community-based providers.
- Translating research into practice: a program that includes experts in social marketing, diffusion research, informatics, anthropology, etc., that focuses on organizational change to enable the translation of research into practice.

Dr. Durham closed with remarks about the OCTRI ultimate vision for shared informatics. They are striving to have a virtual data warehouse that includes data from OHSU, the hospitals, and outpatient departments on a platform that is compatible with that of Kaiser from which research databases can be extracted. This would position them to have patient-oriented research generating clinical hypotheses in clinical populations as well as provide a synthesis of research to identify gaps in information, find evidence based practices and guidelines, translate research into practices, and improve population health.

Collaborative Research Network Updates: Clinical Data Acquisition and Standards Harmonization (CDASH) and Trial Bank – Jody Sachs, D.P.M.

Dr. Sachs gave a brief overview of CDASH project and an update on the progress of the CDASH initiative. The project is comprised of nine representative groups with volunteer members representing industry, CROs, academia and government. The project goal is to develop a set of content standards for a basic set of global data collection fields for case report forms that will support clinical research studies. The initial scope of the project is the safety data domains for adverse events and concomitant medications across therapeutic areas. The overarching goal of this project is to provide a standard format for collecting data at investigative sites, across applications and study sponsors. The collaborative groups are currently reviewing basic data collection variables internally, which then will be distributed for the broader public review and comment.

For the update on the Trial Bank Project conducted by Dr. Ida Sim, Dr. Sachs informed the group that this initiative is no longer active. Dr. Sim wishes to thank the Roadmap Investigators for their support and participation and to let them know that clinicaltrials.gov is working on the registry concept and will continue with efforts related to clinical trial reporting. If Investigators have any comments to contribute to the work of Dr. Sim, please reach her by e-mail: sim@medicine.ucsf.edu

Report on caBig Collaboration – J.R. Landis, Ph.D. & Kevin Peterson, M.D.

Dr. Landis commented that the library of common data elements from National Cancer Institutes (NCI) caBIG project have been downloaded into Penn's system of Oracle Clinical for deployment in pilot studies that are non-cancer studies. As each new study is begun, the common data elements from the non-cancer domains are developed in the case report form layout, for a growing battery of common data elements. Once official curation and transmission process is completed, they will be available in the library. A more detailed report of the success of this effort will be available at the next Steering Committee meeting.

Dr. Peterson commented that with caBIG, they have completed the initial primary care research object model. It is being evaluated for integration into the Biomedical Research Integrated Domain Group (BRIDG) model. Oracle Clinical has been installed for application to the community-based clinical cancer research. A large number of new data elements are being developed and will probably be curated through NCI.

Dr. Peterson requested that Brian McCourt from Duke who has been working with the CDASH initiative, also comment on the development of data elements. Mr. McCourt noted that at Duke they are working on data elements related to cardiovascular disease and tuberculosis. In the CDASH initiative, they are focused on specific domains that are generic, like subject characteristics, demographics, adverse events, with an orientation toward what is commonly collected.

In response to questions from Dr. Peterson and Dr. Sachs, Mr. McCourt outlined the relationship between CDASH, which is an initiative of the Clinical Data Interchange Standards Consortium (CDISC), and HL7. CDISC standards are data structure oriented. CDASH is directed at data content. CDISC and HL7 are working collaboratively. Mr. McCourt specifically noted that HL7, which has been focused on exchanging of physical data, is reorganizing its systems to begin addressing content exchange. He noted that a new Clinical Coordinating committee has been formed recently by HL7 to bring clinical input into the content of the data that is defined in the medical record systems and exchanged. A goal of the committee is to define the issues around the content of the data that is exchanged. They are working on a repository of detailed clinical models, and not just the HL7 message structures of how to send information, but how to represent diverse clinical information. They recognize the need to bring clinical input into that process. Mr. McCourt, who is a co-chair of this HL7 Clinical Coordinating committee, extended an invitation to the Roadmap members to contact him about their organizations participation in the committee.

Report on the Interoperability Working Group – Brian McCourt

Brian McCourt detailed plans for the interoperability working group paper and the mechanisms by which it will be reviewed. The focus of paper will be interoperability and the organization and conceptualization of the twelve different contract's activities within a common scheme.

He noted that one of the challenges faced is identifying the best way to organize information that touches the different areas of interoperability. Information from the previous Steering Committee Meeting Interoperability Group reports, interoperability group survey, quarterly reports and briefing book materials will be used to structure the content of the paper.

Mr. McCourt intends to use information from the current meeting to develop an outline and subsequent draft that represents the robustness of the activities conducted by the 12 Roadmap programs. This outline will be circulated within the upcoming weeks. The target journal for submission will be the Journal of American Medical Informatics Association (JAMIA). As a part of the review process, the paper will be vetted through the Publications Committee with each program PI having the opportunity to comment. Mr. McCourt solicited guidance or comments for this paper.

Collaboration Informatics Demonstration – Dale Hunscher, B.S., & Anthony Leiro, B.S.

Mr. Hunscher and Mr. Leiro presented the challenges to interoperability and provided a demonstration of a central repository tool, (the Velos system) a collaborative project between informatics groups at the University of Michigan and Duke University.

Challenges to Interoperability

- Electronic babel within and across institutions. Informatics people are unable to communicate with clinicians.
- Regulatory issues such as HIPAA privacy rules.
- Organizational silos. Barriers to cooperation and collaboration within and across institutions.
- Prisoner's dilemma.
- Difficulty of distance-based team building. Technologies such as high-speed bandwidth, the Internet, and videoconferencing is lessening that difficulty.

- Psychological barriers such as those that are PI-centric (the inability to envision a personal role in big science initiatives) and the belief that interoperability is difficult and expensive.

Using data from two hypothetical clinical trials at University of Michigan and Duke, Mr. Hunscher and Mr. Leiro demonstrated the use of the interoperability tool. This tool provides a mechanism to gather common data points from the 2 studies from the different institutions without the use of a central data coordinating center. While the systems are different at each institution, information can be shared by being adherent to standards such as HL7 and CDISC.

They noted that technology is not a hindrance to interoperate, but cited that the problems are human-related and can be addressed by working in a standards-compliant fashion which can be achieved in a reasonable period of time at reasonable cost.

Following their presentation, Mr. Hunscher and Mr. Leiro answered questions about the specifics of the system such as capabilities for online electronic informed consent with electronic signature and validation rules.

Roadmap Business Meeting – Jody Sachs, D.P.M

Dr. Sachs announced that the Roadmap Contracts Officer, Mr. Larry Butler, received the no-cost extension requests from all but one principal investigator. Extension requests differ based on contract terms. With the exception of Westat, all contracts will end as of September 2008.

Dr. Sachs gave a brief outline of what is expected for the final Steering Committee meeting (date to be determined). Investigators should talk about their accomplishments and share the lessons learned and information gained, and how it relates to others in the research community. The programs should include how best to disseminate information out to other investigators, and at the national level.

Report from the Communications Committee – Robert Williams, M.D.

Dr. Williams reported that since the December 2006 Steering Committee meeting, the Communications Committee held several conference calls to decide on the best way to disseminate information about the work of Roadmap and decided on producing a paper for publication, preferably in the Journal of the American Medical Association. An initial draft of the paper has been circulated to the Investigator members. He noted that at least two other Roadmap working groups are also preparing to submit papers to the same journal and this raises the question of coordination and how should that be addressed. He commented on the role of the Communications Committee expanding from the original facilitative role to a coordinating role for publications and suggested that the Steering Committee decide what role the Communications Committee should serve.

The Investigators then held discussion regarding the role of the Communications Committee and the submission of papers for publication. Dr. Sachs suggested that the Communications Committee review and comment on all the publications that are going to be submitted jointly.

Principal Investigator Roundtable Discussion – Possible Solutions to Current Network Problems

Dr. Peterson began the discussion by suggesting the group agree on a few things that were learned about developing a network. He focused on the issue of trust as a crosscutting theme to network development and identified issues of best practices.

Dr. Sachs suggested that a tool or metrics to define where the group stands on collaboration would be important feedback to the group. She requested that Paula Lipman from Westat-IECRN address the group to further discuss this idea.

Ms. Lipman noted that network practices vary considerably by types of networks, so classification of network is important, along with looking at what the components within which these networks function, what they are, and how they would collaborate. A metric to evaluate how successful they are could then be considered. Currently IECRN is developing a proposal for this process and it will be circulated to the investigators for comment and feedback.

Sarah Greene from HMORN also commented on metrics. She spoke about the iterative process and the work currently being conducted in NCI by Dr. Kalusny. A Plan-Do-Study-ACT cycle was used on projects within the Cancer Research Network wherein improvement plans were submitted by members based on findings of evaluations.

Discussion was held about issues of trust and relationship building and tools to enable collaboration. Issues related to the people aspect of conducting research and the mechanical aspects of conducting research were given consideration. Assessment of self or assessment of network core infrastructure was suggested as forms of metrics for the people and mechanical aspects of research. Assessment relative to the time it takes to do medical interventions was also recommended. Scientific leadership was considered a critical element, as well as clinical outcome measures such as those found in patient-based metrics and validation tools

Concluding Comments

Dr. Peterson made the distinction between the social and the technical aspects of network success. In summarizing discussions, he identified four major criteria for a successful network in the social realm: trust, communication, mutual benefit or interest, and shared goals. The group concluded as a result of their discussions that they went into the Roadmap CRN initiative thinking that the technical problems would be the greatest challenge, but wound up recognizing that it is the human and behavioral issues that are the greater challenge. Transforming this process at an organizational level requires developing team-oriented models and changing the reward-system.

Closing Remarks

Dr. Sachs adjourned the meeting at 3:30 pm on May 10, 2007.