

**Harmonizing NIH & Industry Sponsored Clinical  
Research Network Architecture  
CRN Harmony**

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

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**BRIEFING BOOK SUMMARY**

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**A. PROGRAM BRIEFING BOOK SUMMARY**

The Roadmap Clinical Research Network (CRN) program at Penn has focused its research endeavor on enhancing the efficiency and productivity in a portfolio of projects, through development and adoption of research technology through the comprehensive use of clinical data management tools. Strides made in these projects have accelerated and strengthened the clinical research process at the University of Pennsylvania. Collaborative efforts among the participating pilot programs have resulted in several focused initiatives to establish research technology and data standards.

**1. PROJECT A: DEVELOP EXPERT-DERIVED CRN RE-ENGINEERING MATERIALS (CRN-REM)**

Oracle Clinical (OC), a comprehensive set of clinical data management tools, is the enterprise resource plan for this project. The OC suite of tools and libraries make information available between modules and among projects for data transactional efficiency. Progressive development and implementation of OC in several different clinical research studies continues with the goal of building and expanding on our OC development experience and introducing OC tools to a wider group of internal and external users at Penn Medicine

**2. PROJECT B: ESTABLISH CRN HARMONIZATION METHODS DERIVED FROM CURRENTLY MERGING NIH-CRNS**

Efforts toward implementation of the Oracle Clinical Adverse Reporting System (AERS) for use in a full-scale, multi-site clinical trial utilization continues with a launch date planned for the fourth quarter of 2007.

Participation of the Penn Clinical Research Network members in the CDISC CDASH (Clinical Data Acquisition Standards Harmonization) adverse event (AE) work stream continues.

**3. PROJECT C: ESTABLISH CRN HARMONIZATION METHODS DERIVED FROM AN INDUSTRY-FUNDED PARTNERSHIP WITH AN ACADEMIC MEDICAL CENTER AND COMMUNITY-BASED PRACTICE SITES**

This epidemiology project is a cooperative effort between the CRCU, the University of Pennsylvania Principal Investigator and an independent Clinical Research Organization, under the direction of the Industry sponsor with guidance provided by the FDA. This network integrates the efforts of industry, an academic medical center, and community-based physician practices to jointly collect and store enrollment, semi-annual, and annual survey data from 5000 participants for a period of up to 10 years. Methodology development compatible with industry and academic medical centers is a major focus for this project. Recent upgrades to the data management system, due to software certification and support deadlines have been completed. Analysis of results from recent data quality inspection is underway.

**4. PROJECT D: INTEGRATE EMERGING CRN-REMS TO AN EXISTING, HIGH-VISIBILITY NIH CRN**

This project represents an opportunity to apply the infrastructure developed by Project A and the methodologies developed by Projects B and C. The Roadmap Research Methodologies team has focused on aspects of clinical research productivity that link with Project D. SiteMinder, an Oracle product clinical management software tool designed to facilitate research management of non-clinical aspects of clinical research, continues in testing at select UPenn clinical sites for the Chronic Renal Insufficiency Cohort (CRIC) Study. Testing and development of standard reports for research projects at Penn utilizing SiteMinder will continue through the next quarter.

**5. PROJECT E: RESULTS DISSEMINATION, TRAINING, AND REPEATED APPLICATION**

CRN Re-Engineering Material (REMs) and results will be disseminated via the the Office of Human Research (OHR) informational infrastructure currently utilized for propagating research standards and training personnel. This effort will be on-going and continuous throughout all years of the project. OHR routinely engages in clinical research training of personnel at UPenn.

The Office of Human Research (OHR) has initiated a training program for clinical investigators that is focused on research operations and regulatory compliance. This comprehensive one-day training, held in April 2007, presented a practical and solution-oriented focus on the topics. In conjunction with this training session, OHR invited several research service centers within the University of Pennsylvania to participate in the "Penn Research Resources Exhibition," providing groups the opportunity to demonstrate their products and services and meet one-on-one with the investigators.

Collaborative efforts with the Abramson Cancer Center (ACC) at the University of Pennsylvania, (a caBIG designated site) continue to pilot the development of cancer clinical studies using Oracle Clinical (OC).

## **B. BUILDING COLLABORATION FOR CLINICAL RESEARCH NETWORKS**

The University of Pennsylvania Roadmap Program brings together a highly productive and talented team of clinical research investigators, already actively involved in the leadership of several NIH-funded multi-center, multi-protocol CRNs, with expertise in biostatistics, clinical epidemiology, data coordination and the conduct of multi-center clinical research networks, informatics and research enterprise architecture. This environment has allowed for collaborations across different projects and groups, both internal and external to the core projects in the University of Pennsylvania Roadmap Program. These collaborations utilize common CRN tools and methods being used across the various projects in the program.

### **1. ABRAMSON CANCER CENTER COLLABORATION**

The UPENN Roadmap program initiated a collaborative effort with the Abramson Cancer Center at the University of Pennsylvania, which is a caBIG designated site, to work together to initiate an instance of Oracle Clinical (OC) in each of these separate environments. The objective in this shared effort is to capitalize on knowledge and experience gained as the ACC develops cancer clinical trials and the Clinical Research Computing Unit (CRCU) develops trials in areas other than cancer.

The Biomedical Informatics Facility (BMIF) staff in the ACC has provided assistance in project planning focused on standardized procedures for development of a data management system for new studies in OC. The BMIF OC pilot project is a breast cancer study. The CRCU is simultaneously developing the testosterone/growth hormone study in OC. This partnership expands the CRCU capacity to coordinate changes with the caBIG standards group.

Development of the first clinical trial in OC (Testosterone, growth hormone and improved bone structure) with creation of study CRFs and utilizing elements of the C3D global library, where applicable has been completed. New data elements specific to endocrinology, testosterone and growth hormone were added to facilitate the study. Data entry and verification have been documented for 13 patients in this trial, which is being conducted over the course of 5 years. In total, 17 new CRFs have been designed and developed in OC.

#### **Challenges:**

- Development of data modules and standardization of processes used in customized data capture instruments.
- Collaborative technologies for integration of data across multiple scales/instruments and agreement on how to interoperate between multiple data formats.
- Creation of uniform data collection and querying systems.

## **2. MERGING NIH-CRNS**

Commonalities identified in treatment of disease symptomatology have prompted Investigator efforts toward development of a joint clinical trial in the CRNs. This has resulted in the establishment of harmonization methods between two separate, multi-center NIDDK-sponsored CRNs -Chronic Prostatitis/Chronic Pelvic Pain (CP/CPP and Painful Bladder Syndrome/Interstitial Cystitis (PBS/IC). This presents additional opportunities for advancing standardization of operating procedures and study conduct methodologies.

CRCU developers have collaborated with Oracle engineers to evaluate and redesign processes surrounding the collection of adverse event data such as collection methods, data processing, coding, and reporting. This included an examination of data credibility issues in the Academic Health Center AE cycle, and comparison of this cycle to that used in the pharmaceutical industry. The result is an extensive change to the system model.

In May 2006, the Penn group coordinated and participated in the Federal Adverse Event Task Force (FAET), focus group in Bethesda, MD. The FAET was convened to develop policies and mechanisms leading to greater harmonization of federal adverse event reporting requirements. The Task Force is comprised of representatives from agencies with regulatory or oversight responsibilities for clinical research.

The FAET convened this focus group to examine current practices in the adverse event process at research sites. Topics discussed by the focus group included reporting problems experienced by investigators, differences in procedures for single-site versus multi-site trials, the problem of confusing terms and definitions, optimum flow of information, and suggestions as to how the federal government can facilitate a streamlined process. In October 2006, Penn joined the CDASH Adverse Event Work Stream focusing on a standardization initiative with the FDA, NIH, several pharmaceutical industry and academic medical center partners to develop a set of 'content standards' (element name, definition, metadata) for a core set of global data collection fields that will support clinical research studies. The initial scope will be the safety data domains.

### **Challenges:**

- Methodological differences in acquisition and detection of adverse event information (diagnostic tests; review of systems approach; adverse drug event questionnaire; prompted vs. unprompted assessment questions)
- Variability in procedures and methods of causality assessment in adverse drug reaction
- Subjective observation vs. objective observation; over-reporting of event vs. under-reporting of event; adverse event vs. co-morbid condition

**Tools:**

- Oracle Clinical Adverse Event Reporting System (AERS) and Remote Data Capture (RDC)
- CDASH Adverse Event Work Stream

**3. PARTNERSHIP WITH AN ACADEMIC MEDICAL CENTER AND COMMUNITY-BASED PRACTICE SITES**

The Pediatric Eczema Elective Registry (PEER) project, a large-scale (4,000 pediatric participants), industry-sponsored disease (atopic dermatitis) CRN which is a partnership between industry (Novartis), an academic medical center (University of Pennsylvania), and hundreds of community-based practices (nationally dispersed) for a ten-year observational cohort study of rare outcomes. Participants have been recruited through a network of 810 referring Dermatologists, Pediatricians, Allergists, Primary Care Practitioners. Participants will be followed for ten years.

**Challenges:**

- Data collection procedures, instruments and storage types across collaborating environments requiring a systematic approach.
- Reporting systems may change across time and technological advances during the length of the project.

**BEST PRACTICES**

Academic collaboration with industry, community practitioners, and governmental institutions bears considerable promise for research best practices. For many complex research projects, we have found that university and external collaborative partnerships are essential to achieving project success. A balance between the benefits of research, the level of resources required for effective collaborative efforts, and funding of research efforts for sustainability is integral in establishing and maintaining best practices for academic collaborative research.

## C. ROADMAP PRESENTATIONS AND PUBLICATIONS

### PRESENTATIONS:

Two posters were presented at the Inventory and Evaluation of Clinical Research Networks (IECRN) National Leadership Forum in Rockville, MD, on June 1, 2006. These presentations highlighted the collaborative partnership between the Penn biomedical informatics initiatives in the Clinical Research Computing Unit (CRCU), and the Abramson Cancer Center and the National Cancer Institutes caBIG program, as well as the developing enterprise between the Penn CRCU, Office of Human Research (OHR) and Oracle Corporation surrounding the development and revision of the Adverse Event Reporting System (AERS®) utilized for comprehensive safety reporting of clinical research studies.

J R Landis, R M Curley, G Fromell, D A Fenstermacher, K Buetow. Emerging Partnership between NIH Roadmap Clinical Research Network and caBIG.

R Landis, R M Curley, W Dyer, M M Becci, S Durborow, M Bigliardo, R Madigan, C Helker, and G Fromell. Emerging Partnership Between NIH Roadmap Re-engineering of CRNs