Translational Medicine and Therapeutics:
The Future of Drug Development

Symposium: May 5- 6, 2006

"Integrated Biomedical and Clinical Research Informatics for Translational Medicine and Therapeutics"

J. Richard Landis, PhD

Robert M. Curley, MS

Gregg Fromell, MD

Center for Clinical Epidemiology and Biostatistics (CCEB)
Office of Human Research (OHR)
University of Pennsylvania School of Medicine
Philadelphia, PA 19104-6021

CCEB

http://cceb.med.upenn.edu/main/index.html

Center for Clinical Epidemiology and Biostatistics

Department of Biostatistics & Epidemiology

CCEB

38
4

education
research
people
biostatistics
epidemiology
community health
services

University *of* Pennsylvania
School *of* Medicine

news • seminars • careers • cceb intranet

CCEB

2

OFFICE OF HUMAN RESEARCH
University of Pennsylvania School of Medicine

The Office of Human Research (OHR) seeks to promote human research for the advancement of healthcare while ensuring the highest level of research participant safety and facilitating the highest quality research by:

- Realizing the best research standards through adherence to University and government research policies and regulations
- Supporting investigators and research teams through process improvement, innovative technologies, and education and training initiatives
- Propagating best operational practices to maximize the efficiencies of research activities
- Collaborating with University organizations involved with human research

CCEB

3

Introduction

- NIH increasingly promotes translational collaborations among basic science and clinical research programs

- <u>SCCORs, PPGs, U01s</u> illustrate interplay of translational science, requiring data integration across the entire research enterprise (basic, translational, clinical)

- ***Biostatistics --*** fundamental challenge at the data analytic stage, incorporating data elements from all sources into comprehensive risk and/or efficacy models

- ***Data management systems*** -- typically isolated, not inter-operable -- inadequate to support biomedical research informatics needs at Research Enterprise level

Introduction (cont'd)

- Successful conduct of clinical and translational science requires biomedical and clinical research informatics **i) methods, ii) tools, and iii) fully integrated informatics highway**

- ***Integrative Informatics --*** despite considerable progress in specialized areas of bioinformatics to harness complex genomics, proteomics and lipidomics data structures, the challenges associated with supporting an integrated (biomedical, clinical research, and health system informatics) clinical and translational science research enterprise are formidable

Challenges

- ***Data Integration*** -- most foundational challenge is the need for an integrated data infrastructure spanning fully the genotype and phenotype (i.e., molecular and clinical attributes) of research subjects and patients
- ***Individual Data Record*** -- relevant data from the basic science, translational, clinical research, and health care domains need to be fully integrated at the individual data record, in order to produce "personalized medicine" models

6

Challenges (cont'd)

- ***Motivating example*** -- consider how the withdrawal of Vioxx and Bextra (due to recognition that they confer a small, but absolute incremental cardiovascular risk) presents a problem for celebrex and new cox-2 inhibitors, such as prexige (lumiracoxib) and arcoxia (etoricoxib)

- Wish to harvest recognized efficacy, but also manage the overall increased absolute risk

7

Challenges (cont'd)

- Translational researchers want access to multiple data enterprises to produce refined estimates of **risk** and **efficacy** at the **individual patient** level

- Data are required from the …
  - Basic Science Research Enterprise,
  - Clinical Research Enterprise, and
  - Clinical (Health Care) Enterprise

Challenges (cont'd)

Basic Science Research Enterprise:
- phenotypic data collected in model systems – e.g., zebrafish, in which the coxs have been genetically manipulated, or in which COX mutations have been detected, or in mice treated with cox-2 inhibitors, in which COX-2 or COX-1 have been manipulated (knocked out, knocked down, globally or selectively, or over-expressed) may inform human genomic association patterns

Challenges (cont'd)

Basic Science Research Enterprise (cont'd):

- cellular imaging data from model systems in which COX-2 has been manipulated (deleted, over-expressed of knocked down) may also contribute insights

- lipidomic analyses of the consequences of COX manipulation in cells, tissues from mice, fish or people in body fluids may provide insights into clinical applications

Challenges (cont'd)

Clinical Research Enterprise:

- individual data from randomized trials and / or observational studies relating to CV events, GI toxicity and concomitant therapy;

- Patient samples for analysis of drug levels and biomarkers of response / risk;

- individual response data, such as efficacy and/or blood pressure data;

- more detailed studies of drug response in small numbers of patients within GCRC setting.

Challenges (cont'd)

Patient-specific Risk / Efficacy Models
-- goal of personalized medicine is the day when each potential patient could say …

"this is the particular drug that works specifically for me"!

12

Challenges (cont'd)

- Disease-specific data integration efforts have led to narrow-scope tools utilizing centralized and highly specific data warehouses

- *Data Integration* – to be transformational, clinical and translational medicine research needs comprehensive **disease-independent**, enterprise-wide data integration and analysis approaches, in order to achieve personalized medicine goals

CCEB

13

Challenges (cont'd)

Breadth of this undertaking necessitates …

- a federated data acquisition, storage and analysis strategy

- an enterprise-wide commitment and investment in a comprehensive vision

- a complex technology base with interoperable data standards and systems

- talented, multi-disciplinary personnel dedicated to realizing this vision

CCEB

14

Vision

This talk will promote a vision for a transformed enterprise-wide informatics framework for the conduct of clinical and translational science ...

- a centralized computational architecture and research data facility

- an integrated biomedical and clinical research informatics toolkit

- an integrated biomedical informatics highway with connectivity among all data repositories

CCEB

15

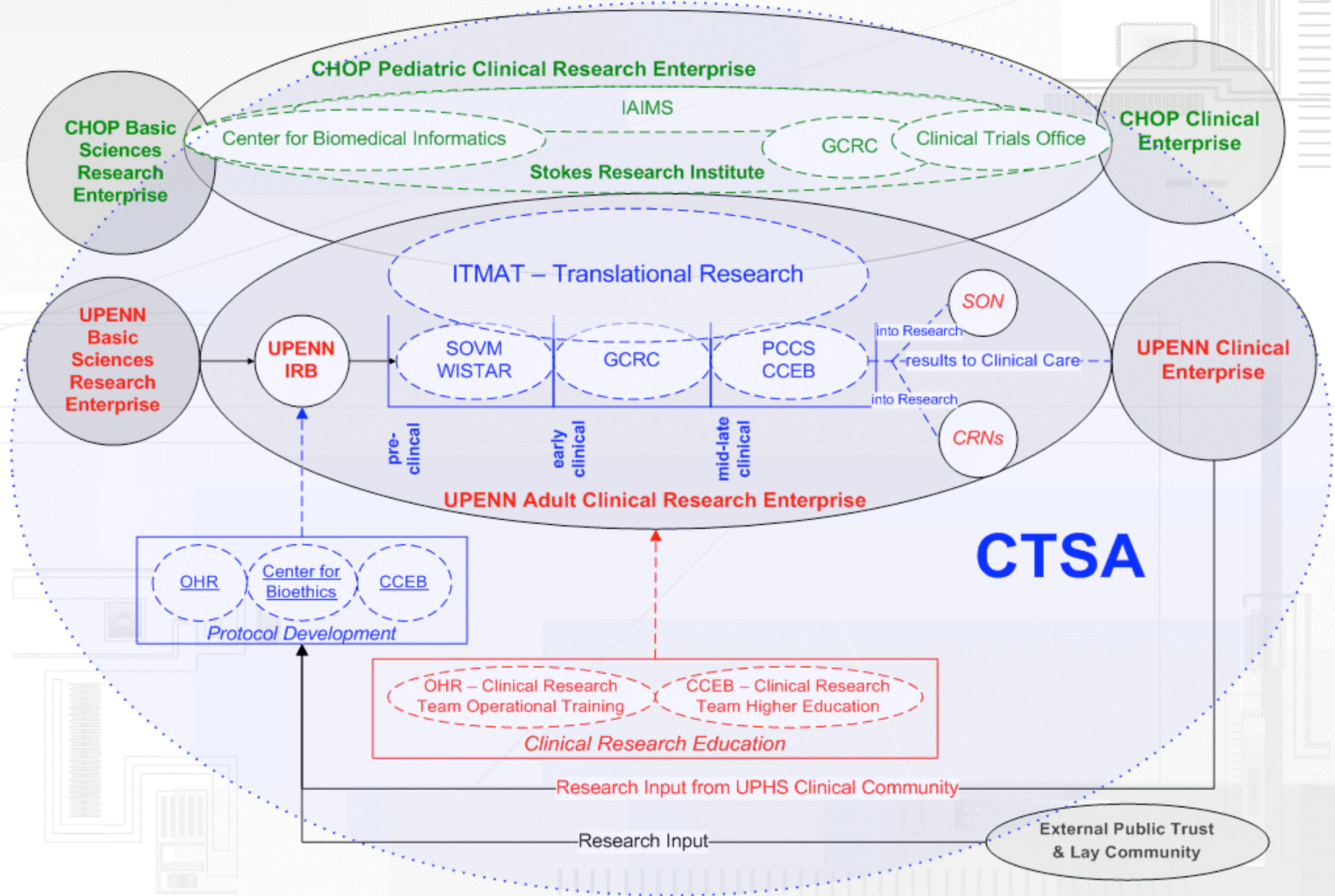# Vision: A New Center for Biomedical Informatics in Translation (BIIT)

Multi-disciplinary team of faculty investigators and technology leaders
- biostatistics,
- bioinformatics,
- biomedical/clinical research informatics,
- computer science, and
- computational biology.

Enterprise Architecture Planning for Clinical and Translational Sciences Award (CTSA)				
Draft	2.4.	NIH NCRR Specification & Requirements for CTSA Applicants	DEC.05	UPENN.SOM.UPHS

CHOP Pediatric Clinical Research Enterprise

IAIMS

CHOP Basic Sciences Research Enterprise

Center for Biomedical Informatics

Stokes Research Institute

GCRC

Clinical Trials Office

CHOP Clinical Enterprise

ITMAT – Translational Research

SON

UPENN Basic Sciences Research Enterprise

UPENN IRB

SOVM WISTAR

GCRC

PCCS CCEB

into Research

results to Clinical Care

into Research

CRNs

UPENN Clinical Enterprise

pre-clinical

early clinical

mid-late clinical

UPENN Adult Clinical Research Enterprise

OHR

Center for Bioethics

CCEB

Protocol Development

CTSA

OHR – Clinical Research Team Operational Training

CCEB – Clinical Research Team Higher Education

Clinical Research Education

Research Input from UPHS Clinical Community

Research Input

External Public Trust & Lay Community

Vision: Center for Biomedical Informatics in Translation (BIIT)

BIIT will provide …..
- new informatics connectivity between CHOP and PENN, permitting enterprises to attain commitment to data interoperability, integration, and sharing between institutions;
- provide comprehensive research informatics support for the biostatistical methods and statistical genetics research computing and data analyses required for enterprise-wide clinical and translational science.

Enterprise Architecture Planning for Clinical and Translational Sciences Award (CTSA)
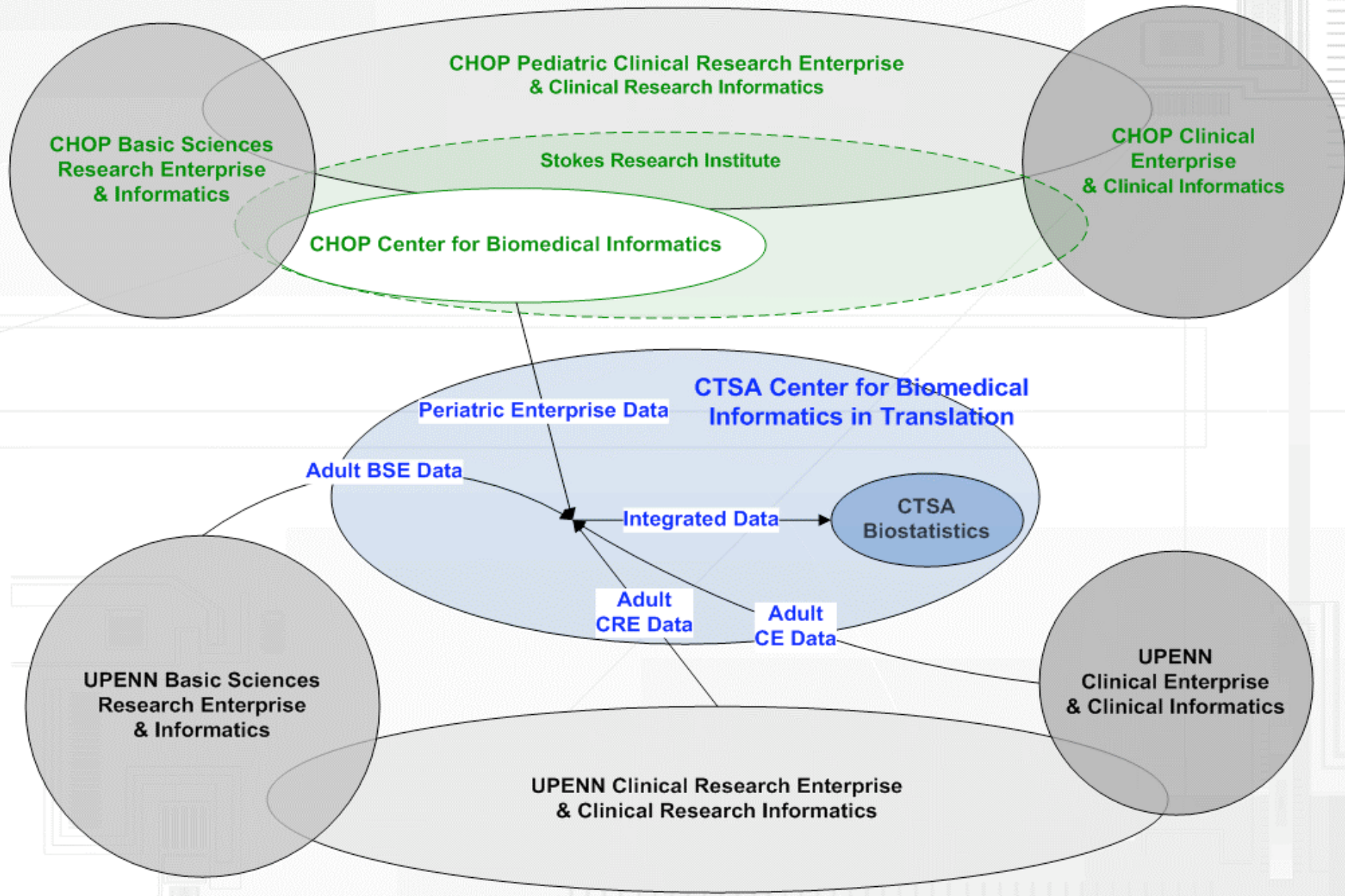
Draft	2.5.	CTSA – Organization of Informatics	FEB.05	UPENN.SOM.UPHS

CHOP Pediatric Clinical Research Enterprise & Clinical Research Informatics

CHOP Basic Sciences Research Enterprise & Informatics

Stokes Research Institute

CHOP Clinical Enterprise & Clinical Informatics

CHOP Center for Biomedical Informatics

CTSA Center for Biomedical Informatics in Translation

Periatric Enterprise Data

Adult BSE Data

Integrated Data

CTSA Biostatistics

Adult CRE Data

Adult CE Data

UPENN Basic Sciences Research Enterprise & Informatics

UPENN Clinical Enterprise & Clinical Informatics

UPENN Clinical Research Enterprise & Clinical Research Informatics

Vision: Center for Biomedical Informatics in Translation (BIIT)

BIIT will provide …

- a ***PENN Center for Clinical Research Informatics*** – an enterprise-wide organization formed to coordinate clinical research informatics standards, tools and the conduct of clinical research studies; enhanced coordination and connectivity between clinical, clinical research, and basic research units and groups within CHOP, leveraging its ongoing efforts in informatics;

- a ***PENN Research Data Center*** – a consolidated facility for biomedical and clinical research informatics resources, with coordinated, centralized IT resources and services;

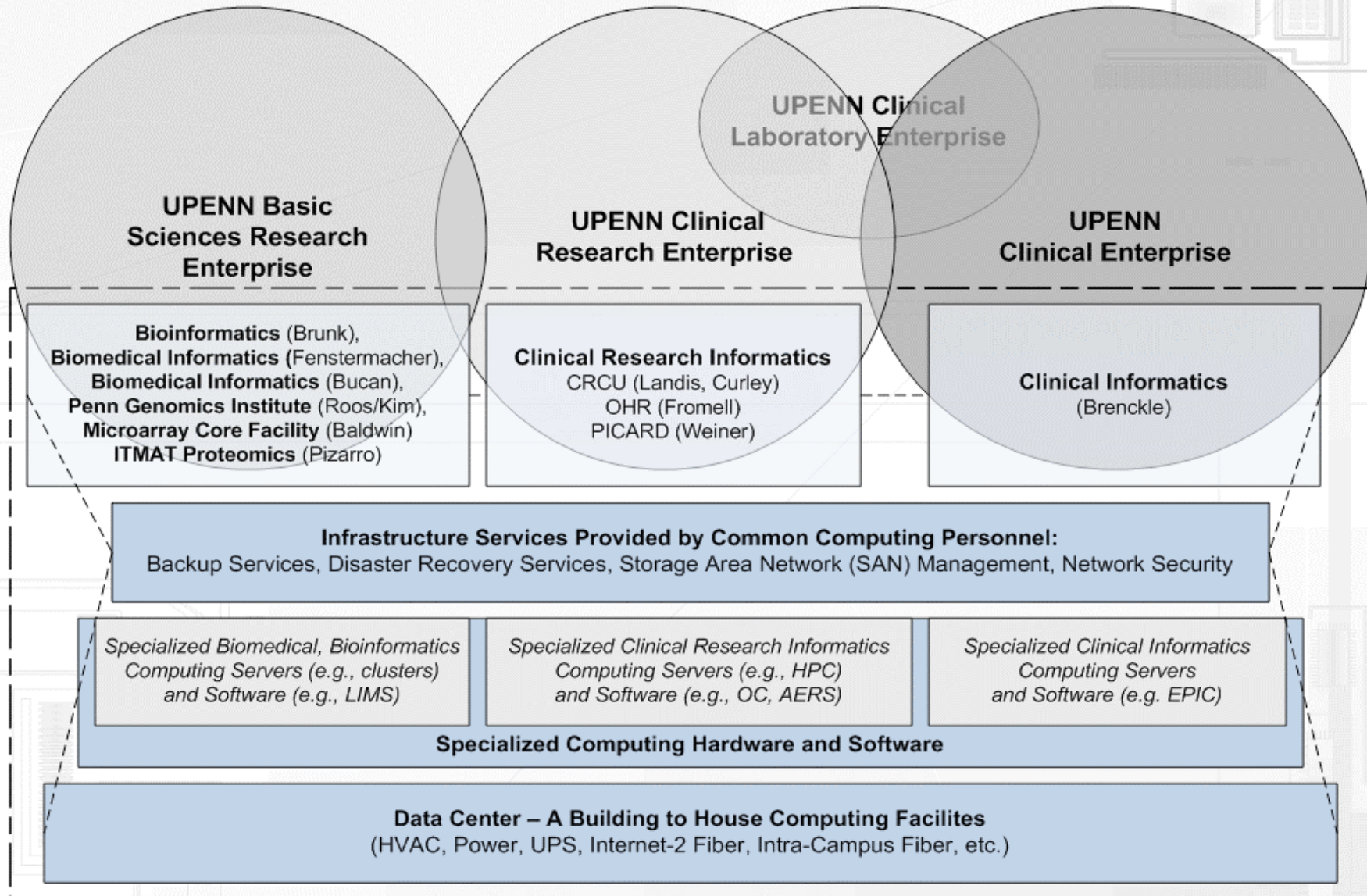**Enterprise Architecture Planning for Coordinated CTSA Informatics**

Draft	2.4.	Enterprise Data Workspaces and Integrated Informatics	FEB.05	UPENN.SOM.UPHS

UPENN Clinical
Laboratory Enterprise

**UPENN Basic
Sciences Research
Enterprise**

**UPENN Clinical
Research Enterprise**

**UPENN
Clinical Enterprise**

Bioinformatics (Brunk),
Biomedical Informatics (Fenstermacher),
Biomedical Informatics (Bucan),
Penn Genomics Institute (Roos/Kim),
Microarray Core Facility (Baldwin)
ITMAT Proteomics (Pizarro)

Clinical Research Informatics
CRCU (Landis, Curley)
OHR (Fromell)
PICARD (Weiner)

Clinical Informatics
(Brenckle)

Infrastructure Services Provided by Common Computing Personnel:
Backup Services, Disaster Recovery Services, Storage Area Network (SAN) Management, Network Security

Specialized Biomedical, Bioinformatics Computing Servers (e.g., clusters) and Software (e.g., LIMS)	*Specialized Clinical Research Informatics Computing Servers (e.g., HPC) and Software (e.g., OC, AERS)*	*Specialized Clinical Informatics Computing Servers and Software (e.g. EPIC)*

Specialized Computing Hardware and Software

Data Center – A Building to House Computing Facilites
(HVAC, Power, UPS, Internet-2 Fiber, Intra-Campus Fiber, etc.)

Vision: Industry Partnerships

- **Oracle Corporation and Penn CTSA –**
  - **Oracle Clinical (OC) Trials Applications**

    … a comprehensive clinical data management solution
    - Remote Data Capture (RDC)
    - Thesaurus Management System (TMS)
    - Adverse Event Reporting System (AERS)
  - **Health Care Transaction Base (HTB)**

    … a platform for integration, development, and operation of healthcare applications.

Vision: Industry Partnerships

- Oracle Clinical (OC) -- standardization and control of data definitions and data usage across a large-scale clinical research enterprise, ensuring that data elements are defined, managed, and interpreted consistently
- OC -- integrated suite of applications (Oracle Clinical Trial Applications) supporting clinical research process
  - -- Remote Data Capture (RDC) - enter and manage data from the investigative site
  - -- Thesaurus Management System (TMS) - classify terms against medical dictionaries
  - -- Adverse Event Reporting System (AERS) - manage and report safety data

Vision: Industry Partnerships

- Site participation requires effort such as budgeting, tracking enrollment, scheduling and conducting patient visits, and managing payments. Data may be in disparate systems such as spreadsheets, making it difficult to get a view of trials underway, exposed the site to inaccuracies, and leading to delays as information is reconciled that can affect the conduct of the trial and willingness of the sites to participate in future trials.
- Sponsors, CROs, and sites need tools to manage site information.
- Oracle offers an application for tracking trial administrative and financial data - **SiteMinder** for sites or **TrialMinder** for sponsors and CROs. It includes: (i) site personnel and contact information, (ii) site events such as visits, (iii) management of patient scheduling and visits, (iv) Contracts and budgeting, (v) Payments due and owed, and (vi) Generating and tracking documents.
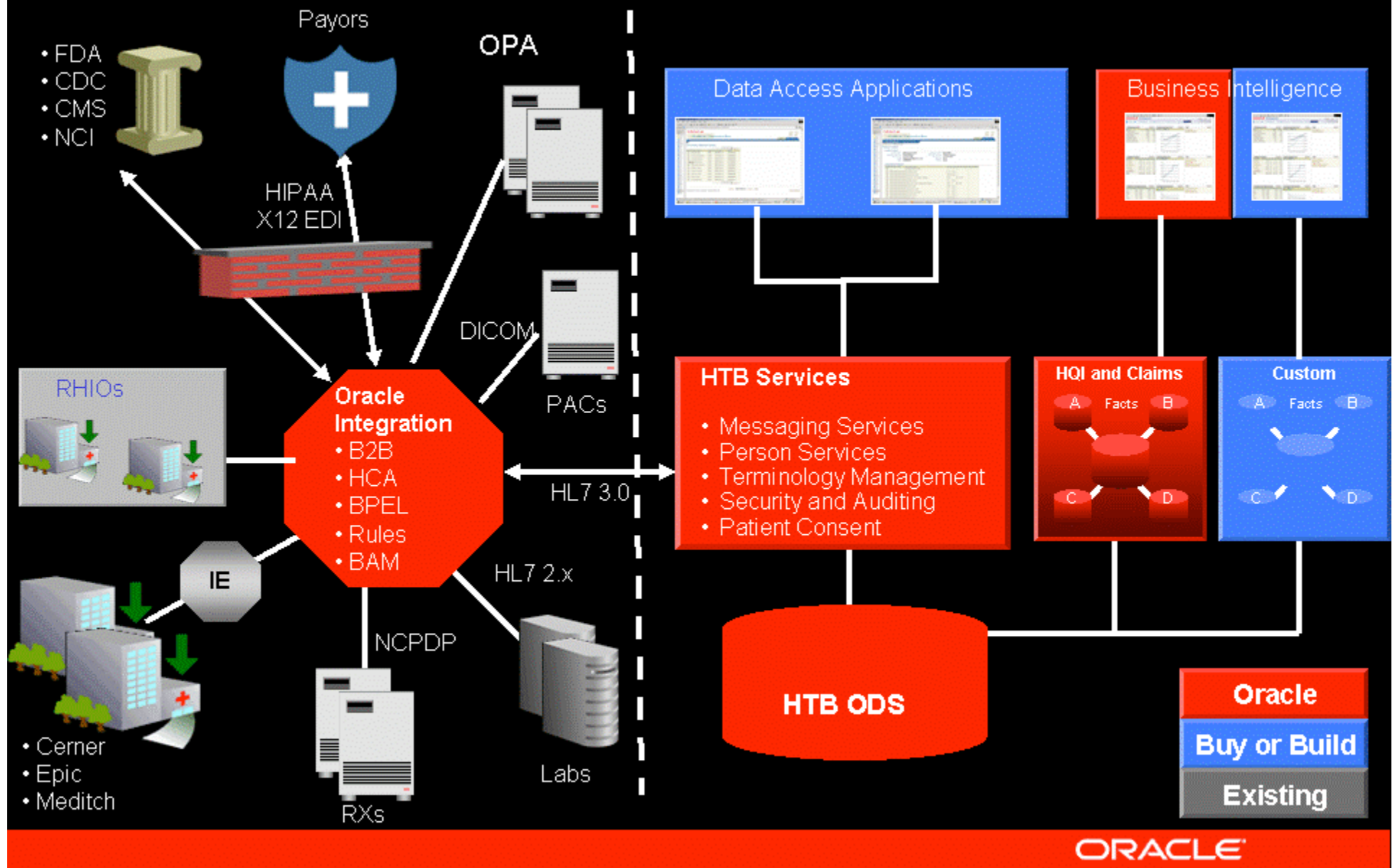
Vision: Industry Partnerships

- Data Integration Models – at the health care enterprise, driven by the business-orientation and compelling business needs for integrated information.

- Lessons learned can be extended to Research.

- An example of a mature Health Care Enterprise solution that could be applicable to research is Oracle **HealthCare Transaction Base (HTB)**

CCEB

25

Vision: Industry Partnerships

- HTB -- platform for integration, development, and operation of healthcare applications
- A comprehensive data repository and standards-based information model, coupled with integrated services for data normalization, customer-defined security and auditing, and business process / workflow.
- Supports meaningful data consolidation and genuine inter-operability among different systems.
- HTB offers a clinical infrastructure based on industry information standards– HL7 version 3 Reference Information Model (RIM)

CCEB

26

Healthcare Integration Conceptual Architecture

Vision: Industry Partnerships

Pharma Partners and Penn CTSA -
a Regional Research
Information Organization (RRIO)

CCEB

28

Vision: Industry Partnerships

- Regional Health Information Organizations (RHIOs) are developing to share data

- Regional Research Information Organizations (RRIO) could be formed for a similar purpose, e.g., GSK and Penn

- Clusters of RRIOs could form the basis for the NIH Roadmap 'National Electronic Clinical Trial and Research Network' (NECTAR)

CCEB

29

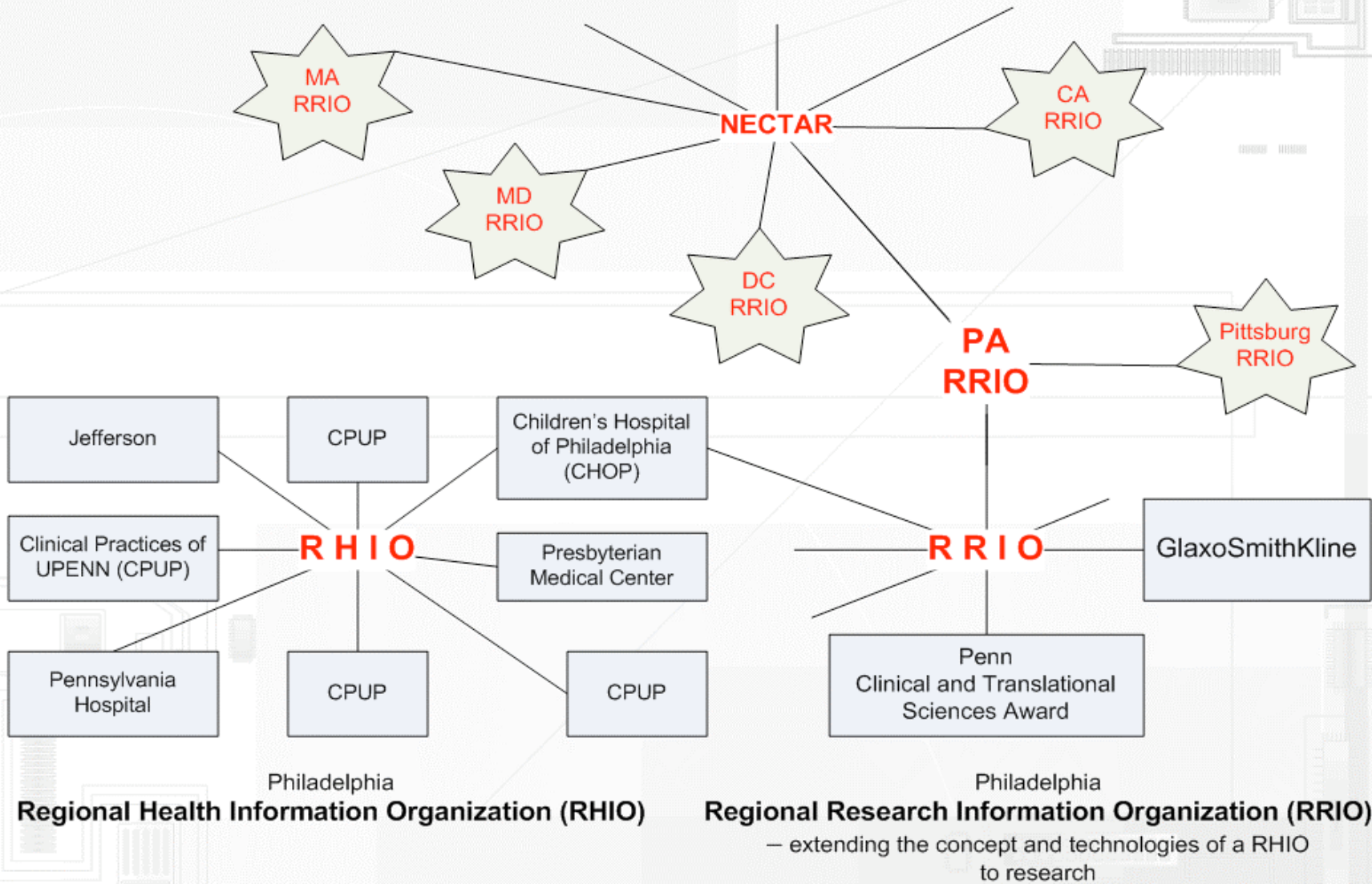**Enterprise Architecture Planning for NECTAR** (National Electronic Clinical Trial and Research Network)

| Draft | 1.1. | Extension of Regional Health Information Organization (RHIO) Concept | FEB.06 | RMC.JRL. |

MA RRIO

CA RRIO

NECTAR

MD RRIO

DC RRIO

PA RRIO

Pittsburg RRIO

Jefferson

CPUP

Children's Hospital of Philadelphia (CHOP)

Clinical Practices of UPENN (CPUP)

R H I O

Presbyterian Medical Center

R R I O

GlaxoSmithKline

Pennsylvania Hospital

CPUP

CPUP

Penn Clinical and Translational Sciences Award

Philadelphia
Regional Health Information Organization (RHIO)

Philadelphia
Regional Research Information Organization (RRIO)
— extending the concept and technologies of a RHIO to research

Conclusions

- Tomorrow's 'translational knowledge' is developing and accumulating today in the foundational form of information and data.

- This information will be converted to knowledge via a 'data organization and analysis partnership' between Clinicians, Investigators, Biostatisticians, and Informaticians.

CCEB