Update: ARRA Comparative Effectiveness Studies- Clinical Trial Repository and PACES Initiative

Science Board Meeting

May 20, 2011
Comparative Effectiveness Research
Patient-Centered Health Research

• The Recovery Act provided $1.1 billion for patient-centered health research, also known as comparative effectiveness research.
  • $400 million to NIH
  • $400 million to the Office of the Secretary (HHS)
  • $300 million to the Agency for Healthcare Research and Quality (AHRQ).
• The goal of this research is to promote high quality care by providing scientific information that helps clinicians and patients determine the best care that suits their needs.
<table>
<thead>
<tr>
<th>Activity</th>
<th>FDA ARRA CER Scope Description</th>
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<tbody>
<tr>
<td>Development of a Clinical Trial Repository</td>
<td>• Support the software development life-cycle phases of requirements and design analysis, development/enhancement, testing, training, and implementation.</td>
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<tr>
<td>Convert Legacy Data</td>
<td>• Convert legacy data from clinical studies relevant to specific questions of comparative efficacy to a standard format harmonizing terminologies as needed and storing the standardized data in the data repository.</td>
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| Implement Modern Analytical Tools            | • Support comparative effectiveness research using the clinical study data repository.  
• Provide integration and implementation support for selected tools.                                                                                                           |
| PACES                                        | • Facilitate comparative analysis pilots to conduct advanced and robust analysis for detecting clinical trends to understand which interventions are most effective for which patients under specific circumstances.  
• Establish Partnership in Applied Comparative Effectiveness Science for Medical Products (PACES).  
• Host public scientific workshops to discuss analytic tools, methods, and best practices for analyzing data across multiple clinical studies |
The Vision- ARRA project to found FDA Science Computing

- FDA has been working towards an electronic approach to acquire, receive, and analyze study data
- Electronic capture of study data is vital to integrate pre-marketing study data and post-marketing safety data
- FDA is working towards development of a scientific computing environment to support research and a development for our data
The enclave will be a hub for data integration

- "Web of Science"
- ICT21 Advanced Analytics
- Common Electronic Document Room
- Regulated Product Submission
- Emerging Science
- Emerging Events
- Prior reports
- Data
- Decisions
- Lab Results
- Compliance
- MARCS
- Safety Reports
- Prior data
- Who
- What
- Where
- Personal Health Records
- Medwatch Plus & FAERS
- Harmonized Inventory
Scientific Computing Goals

• Institute a regulated product information data warehouse
  – Electronically acquire, validate, integrate, and extract standardized, structured scientific data
  – Synthesize information across product applications, across classes of products, and across product lifecycle
    • For example, new nephrotoxicity biomarker approved in one area could be used for a different product area
    • Ingredient found unsafe or component found defective may be found in other product areas (e.g., combination products, kits, inactive ingredients)
• Transform the regulatory review and decision process
  – Transition to interactive, electronic reviews
    • Support quantitative decision-making to assess safety and effectiveness throughout a product’s life cycle (e.g., data mining to detect possible safety signal)
    • Leverage analysis tools across product areas improving consistency and efficiency
  – Provide springboard to environment of the future that enables
    • Enriched scientific interpretations that integrate latest domain knowledge
    • Advanced analytics (e.g., virtual clinical trials, disease models)
Update: Development of a Clinical Trials Repository

- Collaborative effort with National Cancer Institute (NCI)
- Prime contractor is SAIC-Frederick, operating as a Federally Funded Research and Development Center (FFRDC) under a long term-contract with NCI
- Subcontract for development of the Clinical Repository was awarded to Ekagra Software Technologies, Ltd., on 3/28/2011
- Project duration is through 9/30/2013
Clinical Trials Data Repository
CTR Development Scope & Objectives

- Analyze technical requirements & develop a CTR database to create a common, shared repository capable of meeting FDA’s requirements for comparative effectiveness analysis of clinical study data (e.g., HIV, diabetes, vaccines, devices)
- Fully automate the process of validating and loading SDTM datasets into the CTR
- Implement an operational environment that supports the automatic validation, loading, and management of standard clinical trials data and provides reviewer access to data for CER using the JReview and WebSDM reviewer tools
CTR Development Scope & Objectives (continued)

- Implement a “standalone” version of the SDTM validation service that can be made publicly available to sponsors to validate their datasets using the same criteria that will be applied by the CTR.
- Implement a version of the SDTM validation service in the CTR at NCI to validate datasets prior to loading them into the CTR database.
- Develop, document & implement features to support access management and security functions to allow role-based access to study data in the CTR.
- Ensure that the software development project plan, software code, and system designs and documentation for the CTR are done in compliance with 21CFR part 11 and can be validated following FDA validation practices & guidelines.
## Project Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Estimated Completion Timeframe</th>
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<tr>
<td>Program Baseline Review</td>
<td>May 2011</td>
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<tr>
<td>Data Model Requirements Review</td>
<td>July 2011</td>
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<tr>
<td>Deliver EPLC CTR Detailed Design Review Document</td>
<td>August 2011</td>
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<tr>
<td>Deliver updated Security Plans (SSP), Security Risk Assessment (SSA)</td>
<td>October 2011</td>
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<td>Load and Validation Service Installation</td>
<td>October 2011</td>
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<td>Deliver Test Package</td>
<td>November 2011</td>
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<tr>
<td>Prepare SDTM materialized views</td>
<td>November 2011</td>
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<tr>
<td>Deliver installation demo to SAIC-F</td>
<td>December 2011</td>
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<tr>
<td>Validation Service in staging or production</td>
<td>January 2012</td>
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<tr>
<td>Production database ready for CER analysis</td>
<td>January 2012</td>
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<td>Estimated Completion Timeframe</td>
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<tr>
<td>Implement ETL process</td>
<td>March 2012</td>
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<tr>
<td>Load Services in staging or production</td>
<td>September 2012</td>
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<tr>
<td>Implement Dashboard software</td>
<td>October 2012</td>
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<tr>
<td>Implement Dashboard software</td>
<td>November 2013</td>
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<tr>
<td>Complete System Integration</td>
<td>December 2012</td>
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<tr>
<td>Complete Integration / Regression Testing</td>
<td>January 2013</td>
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<tr>
<td>Operational CTR Solution</td>
<td>March 2013</td>
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<tr>
<td>Complete Study Data Submission Support</td>
<td>September 2013</td>
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<tr>
<td>Finalize Training and Testing</td>
<td>September 2013</td>
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<tr>
<td>Operational CTR Solution – Final Deployment</td>
<td>September 2013</td>
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<tr>
<td>Deliver Project Summary Report</td>
<td>September 2013</td>
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Partnership in Comparative Effectiveness (PACES)

Pilot program to conduct PCOR in full collaboration with FDA scientists and reviewers
High Level Project Overview


Clinical Design (#1)
Clinical Design (#2)
CER Study (#1)
CER Study (#2)

Workbench development

All projects in collaboration with the investigators at the FDA who are experts in the content area of the data we will be using.
Trial Designs Targeted at Estimating Treatment Effects in Subpopulations

Dr. Michael Rosenblum - Lead
Department of Biostatistics
Goal:

To promote early consideration of adaptive designs and methods/tools for knowing in what situations they might be most useful.
Why Adaptive Designs

Potential Benefits:
- Can yield studies with more power and allow determination of subpopulations that benefit most
- Can reduce cost, duration, and number of subjects of trials

However, MUST:
- Control probability of false positive results
- Maintain study integrity
- Minimize bias/ maintain internal validity
Types of Adaptive Designs to Select

Consider applications where:

- Few subpopulations (e.g. having a gene variant or not);
- Moderate number of subpopulations (e.g. 10 levels of a biomarker);
- Large number of subpopulations (e.g. many baseline risk factors to choose from).

Will begin with trials of medications for treatment of HIV infection.
Tools we will generate:

• Analytic tools to prove strong control of familywise Type I error rate, and to bound bias and mean squared error

• Software tools to compare power of adaptive versus fixed designs in data-driven scenarios

• Should be useful to FDA and industry for the design/conceptual phase of the study
Application of Bayesian Nonparametric Methods to Population Pharmacokinetics and Pharmacodynamics

Dr. Gary Rosner - Lead
Oncology Biostatistics and Bioinformatics
Background

• Comparative effectiveness research often requires *combining* relevant data from disparate sources

• Context comes from using information from other studies and data where the treatment is used in a broader population than in trials

• Bayesian inferential paradigm = structured way to combine information from disparate sources
Specific Aims

Aim 1: Develop flexible mixture prior models -- Bayesian nonparametric hierarchical model

Aim 2: Develop & test models using the FDA data supplemented by other data

Aim 3: Simulation studies to compare the method to several alternatives
Advantages of Bayesian Inference

- Easier to incorporate external information (such as from a registry or observational study) or historical data from earlier trials

- Follows learning paradigm

- Easier to account for sources of uncertainty

- Prediction is straightforward
Summary

• Mixture models we will develop will allow flexibility when combining data from disparate sources

• Allows for meta-analysis (pooling) of *somewhat* related studies
  – Finite mixture or fully nonparametric models to combine data from related studies

• Can use predictive distribution for parameters from meta-analysis of existing studies as the priors for inference about new (not so closely related) patients

Will use data from the trials of cardiac resynchronization
A comprehensive framework for analyzing heterogeneity of treatment effects (HTE) in comparative effectiveness research

Dr. Ravi Varadhan - Lead
Department of Medicine
Individuals have Multiple Attributes

- Modern approaches can accommodate a multivariate context
- This amplifies the need for careful analysis
- Team developed an analytic framework in a project funded by the Agency for Healthcare Quality and Research
Specific Aims

Aim 1: To apply overall framework to FDA studies involving subgroups, particularly those studies which led to a policy decision affecting a subgroup

Aim 2: To develop and apply statistical techniques to support the framework
   (2a) Multivariate subgroup analysis
   (2b) Bayesian subgroups estimation
Summary

• Provide a useful conceptual framework for subgroups analyses

• Create statistical tools (methods + R package + WinBUGS code) for detecting heterogeneity of treatment effect and estimating subgroup effects and displaying the results

We plan to use trials of osteoporosis treatments
A Systematic Benefit-Risk Assessment: A Multicriteria Decision Analysis using the Analytic Hierarchy Process

Dr. Sonal Singh - Lead
Department of Medicine
Background

- Most studies describe efficacy outcomes (or benefit) and safety outcomes (risk), independently

- Incremental net health benefit of a product *at approval* usually provides sufficient safety margin that a *qualitative* benefit risk assessment suffices

- Need to move from ‘implicit’ to “explicit’ decision-making
Study Aim

To demonstrate application of the Analytic Hierarchy Process for consideration as a useful tool for the FDA
Analytic Hierarchy Process

A Multi-Criteria Decision Analysis

• Allows evaluation of risk-benefit tradeoffs in complex situations

• Allows for quantitative and qualitative input from various stakeholders for decision making with multiple objectives

• Supports judgment by making judgments explicit and transparent
Analytic Hierarchy Process Overview

Step 1: Defining the regulatory decision context
Step 2: Assembling and organizing outcomes
Step 3: Making Comparisons*
Step 4: Combining judgments to see how alternatives meet goal **
Step 5: Sensitivity Analyses

*Comparisons: between drug options and between criteria used to define the balance between benefits and harms; pair-wise comparison

**Combining judgments --- AHP process, combines and weights the judgments in step 3
Summary

• Novel comprehensive systematic approach to systematically address risks and benefits in a transparent patient-centered way

• End of study deliverable: A new toolkit to evaluate benefit and risk during a product’s life-cycle.

We will use trials of diabetes drugs
Summary

• The clinical trial data repository is currently in development with planned initial use by January 2010
• Four major PACES projects are underway
• Many datasets are undergoing conversion and transformation (not discussed)
• IT infrastructure in place and will support greater scientific computing effort
Thank you!