Comparative Effectiveness Research Plan

Science Board Meeting

November 15, 2010

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.

ARRA CER and FDA

- Build FDA CER clinical data and standards infrastructure, tools, skills, and capacity
  1. Harness the capacity of large study data repositories to answer questions about care for priority interventions through infrastructure development
  2. Enable pilots of comparative effectiveness and other complex research and evaluation using the agency's vast, but untapped, stores of patient safety and clinical efficacy data.
  3. Support building needed expertise across the Agency, as well as FDA interactions with NIH, AHRQ and sponsors, as they design and evaluate CER, including needed guidance.
  4. Evaluate policy approaches
  5. Inform and improve medical and regulatory decision making and improve patient outcomes

Activity	FDA ARRA CER Scope Description
Development of a Clinical Trial Repository	• Support the software development life-cycle phases of requirements and design analysis, development/enhancement, testing, training, and implementation.
Convert Legacy Data	• 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.
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

Development of Clinical Repository

Objectives

- Design, develop & deploy a clinical trials repository (CTR) to support FDA comparative effectiveness research (CER) in specific therapeutic areas
- Implement an operational prototype that supports the automatic validation, loading, and management of standard clinical trials data (in SDTM format) in the CTR and reviewer access to that data for CER using (at a minimum) the JReview and WebSDM reviewer tools
- Develop an SDTM Validation Service that can be made publicly available to sponsors so that they can pre-validate datasets in the future using the same criteria that will be applied by the FDA CTR

Long-Term Requirements—beyond the ARRA CER project

- Janus operational pilot for clinical study data will be implemented & hosted at NCI through 2013 under the ARRA CER contract
- Decision on hosting Janus at NCI beyond the $2^{1/2}$ year project has not been determined—future discussions between NCI and FDA should be planned to address future hosting requirements and/or alternatives and associated costs
- Transition of Janus to another site is predicated on the availability of another environment capable of hosting & supporting

Legacy Data Conversion

Background

- Clinical trial data has been collected for many submissions
- Analysis of data from across various trials is difficult
  - Submitted in various non-standardized structures
  - Formats including paper-based
- FDA wants to facilitate meta-analysis across multiple studies
- Certain legacy study data need to be converted into an electronic uniform standard structure to facilitate answering important scientific and regulatory questions of interest to promote the public health.
- The intent is to populate the data warehouse with these datasets in a common “language” or format. This work is fundamental in enabling the success of initiatives to comparatively evaluate product effectiveness.

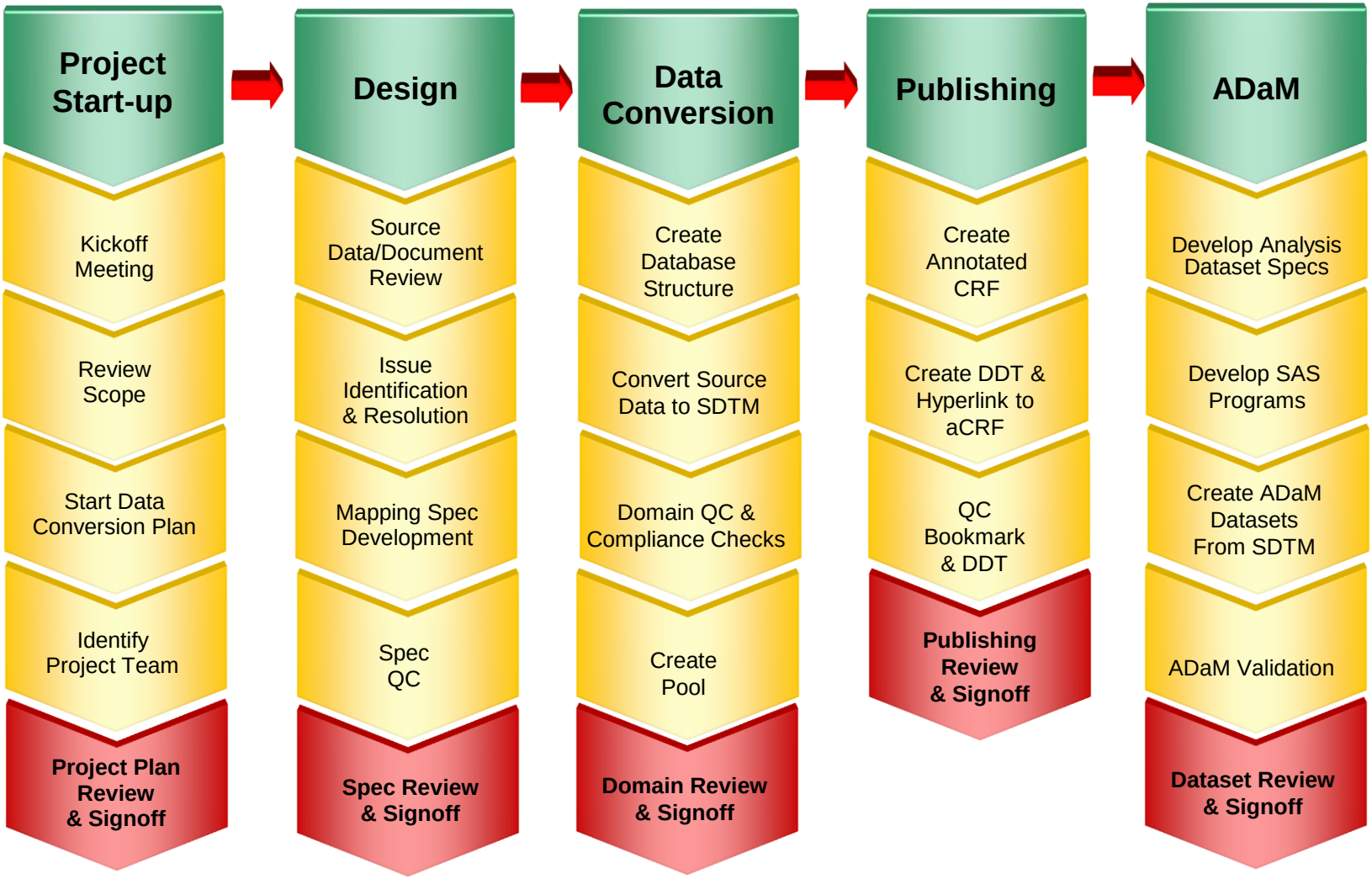
Team Members

SCENPRO	**Program Management** **Richardson, TX** **Lead: Derek Allen**
Octagon Research Solutions, Inc.®	**Data Conversion** **Wayne, PA** **Lead: Donna Derivan**
CDISC	**Data Standardization** **Austin, TX** **Lead: Dr. Rebecca Kush**

Objectives

- Support for the conversion of legacy clinical trial data to the SDTM format
- Creation of analysis data sets to enable exploration of Comparative Effectiveness Research (CER) questions related to vaccines, drugs, and medical devices.
- Convert clinical trials datasets into CDISC-compliant SDTM datasets (v3.1.2) and create analysis datasets in support of CER.
- Accommodate timelines to complete the project tasks

Data Conversion Process Flow



Modern Analytical Tools

Objectives of Modern Analytical Tools

- Provide research computing infrastructure (hardware, software, support staff) needed for scientists to conduct comparative effectiveness research on behalf of the FDA.
  - Reason for FDA's participation in ARRA CER and for it's inclusion of a task for implementing modern analytical tools was to jump start FDA's technical infrastructure for scientific research computing.
  - For CER, could use what FDA already has but would miss the opportunity to move into the 21st Century for scientific research computing.
- Data should be stored consistent with the envisioned data marts that will be ultimately provided as part of Janus (i.e. SDTM and ADaM tables in Oracle)
- Modern analytical software should be configured to take advantage of server speed for both data access and computations
- Network accessible from either regulatory or scientific network and with connectivity to high performance computing

FDA Partnership in Applied Comparative Effectiveness Science Initiative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CER Study 1: A comprehensive framework for analyzing heterogeneity of treatment effects in comparative effectiveness research

Specific Aims: (1) **To test an analytic framework for subgroup analysis** using the CER example of therapy to be determined; (2) To **apply the framework** to thoroughly examine published CER studies that resulted in policy decisions affecting a subgroup.

Will empirically test the value of: **pre-specifying** the subgroups and analytic protocol for testing heterogeneity of treatment effect (HTE), **differentiating exploratory versus confirmatory** subgroup analyses, testing for interactions, **displaying graphically** the HTE results, **validating** subgroup results.

CER Study 2: Systematic Assessment of the Benefits and Risks of a therapy (TBD): A Multicriteria Decision Analysis using the Analytic Hierarchy Process

Specific Aim:

To conduct a **multi-criteria decision analysis** to do a benefit-risk assessment of the thiazolidinediones in individuals with type 2 diabetes relative to sulfonylureas and metformin, using the Analytic Hierarchy Process. (Dolan, 1989; Tsaty, 1994; Singh, 2006; Dolan, 2008)

The Analytic Hierarchy process can flexibly address a range of decisions that involve both **quantitative data** and **subjective input**. The methodology can also be **applied to evaluate medications in the pre-approval period**, with appropriate accounting for uncertainty around the estimates of long term safety. Investigators will: define the decision context; assemble and organize outcome information; make comparisons among the alternatives; combine the results of the judgments; and perform sensitivity analyses.

Clinical Design Strategy 1: Optimal Clinical Trial Designs for Estimating Treatment Effects in Subpopulations

Specific Aim: To develop **statistical methods and software** that will enable investigators and regulators to determine, for a given scenario, the **best trial designs and analyses** for generating evidence about treatment effectiveness in different subpopulations.

Will consider three categories of studies: 1) where the subpopulations of interest are known before the study starts, and there are relatively **few**; 2) where the subpopulations of interest are known before the study starts, and there are **more than a few** such subpopulations of interest; and 3) where the subpopulations of interest are **unknown** before the study starts.

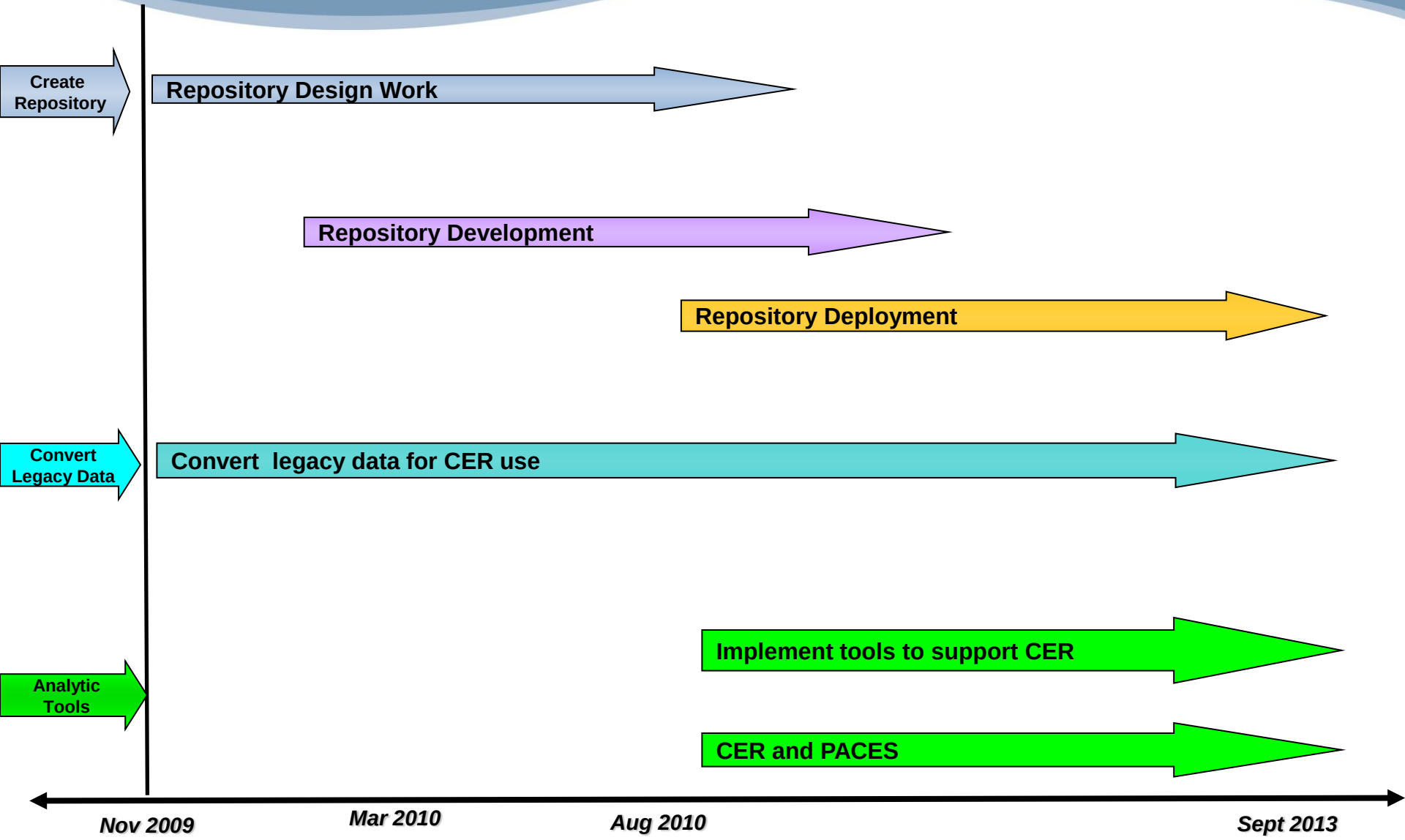
Will construct candidate clinical trial designs aimed at making inferences about specific subpopulations. Will include **group sequential designs with no adaptation**, and group sequential designs that incorporate the following types of **pre-specified adaptations** at interim analyses: **changes in the sample size, changes in the randomization probabilities, and changes in the subpopulations sampled.**

Clinical Design Strategy 2: Improved Design of Randomized Trials with Use of Information from Historical Controls

Specific Aim: To develop **mixture prior models** for use when incorporating **historical control data** with a concurrent control that is part of a randomized controlled trial (RCT).

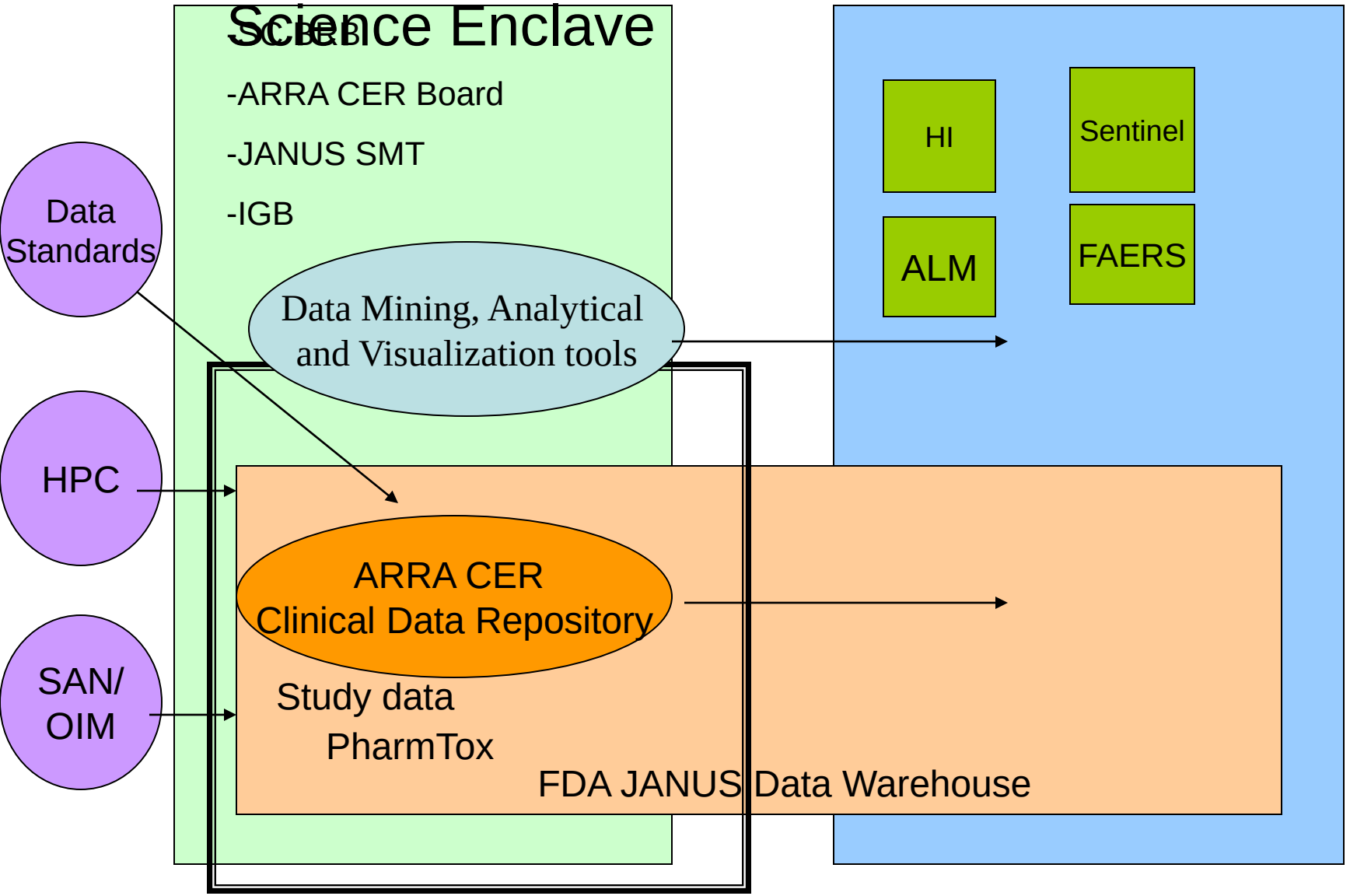
Flexible Bayesian nonparametric models allows one to include more relevant data sources than is possible when using other models; the **mixture approach will be more robust to data-source-specific departures from a common, exchangeable hierarchical model.**

We will **develop and test this model**, using the RCTs in JANUS and data from other databases. We will carry out **simulation** studies to test these mixture prior models and **compare the method to alternative formulations** for incorporating historical data. We will use patient-level data in FDA database, along with complementary data warehoused in these other databases.



Proposed Timeline Assuming ARRA Funding

Regulatory Environment



Upcoming Event

- First FDA-hosted PACES Workshop
  - Internal FDA workshop to determine CER priorities-Feb 3 & 4
- Stakeholder Workshop on CER
  - TBD

Thank you!