A Web-Based Protocol Tracking Management System For Clinical Research

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Abstract

Clinical research approval processes are complex since they involve human subject welfare as well as regulatory and ethical concerns. Typically, clinical research institutions have an elaborate established review process; the labor-intensive and time-consuming nature of this process can result in approval delays thus significantly impacting the biomedical research. This paper describes the development of a web-based information system designed to make the process of protocol approval more efficient, organized, and accurate. The system enables the principal investigators (PIs) to initiate, track and manage clinical studies, monitor review processes, view status changes, and quickly respond to requests for additional information. In addition, it allows the protocol coordinators (PCs) to manage the entire Institutional Review Board (IRB) approval process.

1. Introduction

The Center for Information Technology (CIT) at the National Institutes of Health is in collaboration with the Division of Intramural Research (DIR) of the National Institute of Neurological Disorders and Stroke (NINDS) for the development of an integrated clinical informatics and management system to be used by its intramural clinical researchers. The Clinical Informatics and Management System (CIMS) is a centralized clinical data management and analysis system that will assist clinical investigators in managing protocols and patient and research data as well as in integrating disparate data sources for analysis. The Protocol Tracking Management System (PTMS) is one component of the CIMS application. An overview schematic of CIMS is depicted in Figure 1. CIMS consists the following major components:

- A *Protocol Tracking Management System* (PTMS) that supports protocol submission, approval, and monitoring of protocol review process.
- A *Clinical Study Informatics System* (CSIS) that provides patient data management via protocol setup for patient recruitment, screening, enrollment, dynamic form creation, data collection, monitoring, and reporting.
- A *data integration* module that provides data warehousing services to collect data from a variety of data sources such as external scientific databases; its scope also encompasses analytics tools that will facilitate data mining and statistical analysis of

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data from CIMS as well as the external sources to support biomedical discovery and translational research.

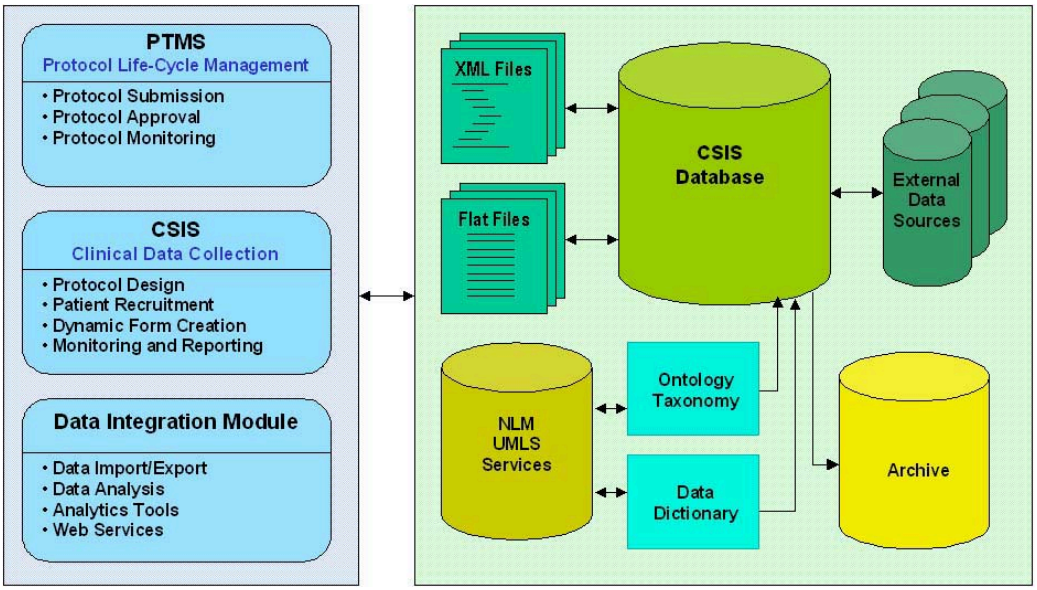

Figure 1: Clinical Informatics and Management System (CIMS) overview schematic

2. PTMS Overview

From the onset of preparing protocol submission, a PI enters her protocol information online, attaches the necessary files to the protocol, and electronically submits the protocol and attachments directly for review. The PI can print the *Clinical Research Protocol Initial Review Application* form, also known as the 1195 form, or other documents. Once her protocol is submitted, the PI can monitor the ongoing status of protocol reviews, and view or respond to comments made on a protocol by a PC, a *statistical reviewer*, or an *IRB primary reviewer* regarding a concern, deficiency or stipulation. The PI can also designate *authorized users* to have access only to view the protocol information, or have access to manage it. However, only a PI is authorized to submit protocols to the IRB committee for review. In addition, a PI or designated authorized user can initiate an Amendment, Serious Adverse Event, Violation, or Termination at any time and the PI can submit these for review electronically. The PI can also view protocols with upcoming Continuing Reviews at any time and enter data for the *Clinical Research Protocol Continuing Review Application* form, also known as the 1195-1 form. Finally, the system automatically sends e-mails to the PI for protocols requiring action.

Figure 2 shows an example workflow and status for a single protocol. The rows represent various review process in a protocol lifecycle. The columns represent series of approval steps that a review has go through. Each cell contains a color-coded status of the review step. By clicking on the cell, investigators and reviewers can see detailed review history, and change review states.

The *protocol coordinator* manages the entire protocol tracking process through the online web application. For example, the PC can manage the status of individual reviews for

protocols, can assign reviews to *statistical* and *primary reviewers*, can associate reviews to IRB and Scientific Review meetings, and can record submissions and approvals of protocols to and from Protocol Services. The PC can add minutes and stipulations for a review based on an IRB or Scientific Review meeting, as well as add new meetings into the system and schedule protocols for review. The PC can also view lists of protocols that are newly submitted, that have upcoming Continuing Reviews, or are designated for PC action. Lastly, the system automatically sends e-mail messages to the PC for protocols requiring action.

The PC also manages the users of the PTMS system. The PC can add or delete users, and can also assign one or many roles to a user. The PTMS system includes roles such as PI, PC, *Statistical Reviewer* (SR), and *Primary Reviewer* (PR). Users assigned to these roles can receive e-mail messages for protocols requiring action. Other roles in the PTMS system include *Branch Chief* (BC), *Scientific Director* (SD), *IRB Chair*, and *Clinical Director* (CD). The Statistical Reviewer can access assigned reviews and perform approvals or other actions on a protocol electronically. The Primary Reviewer can access assigned reviews. The Branch Chief can view any protocols created by the principal investigators in his or her branch. The *Scientific Director*, *IRB Chair*, and *Clinical Director* can all view any protocols and their status at any time.

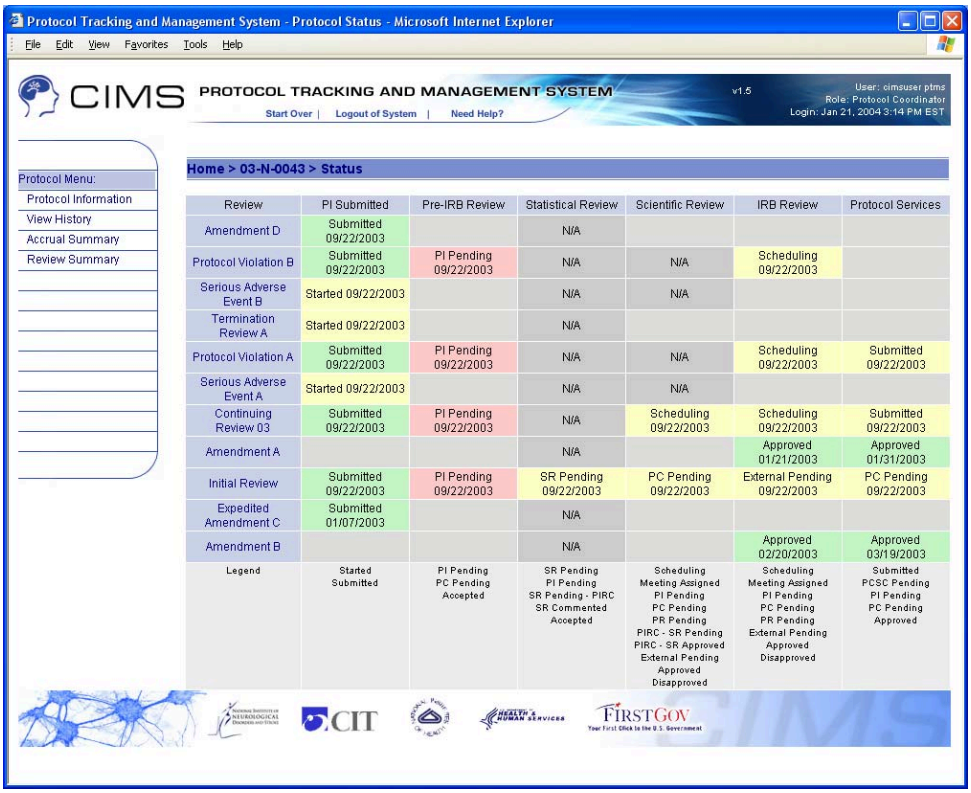

Figure 2: Protocol review workflow and current status.

3. Architecture Design Framework

Since the CIMS system needs to support various client computing platforms, it has been designed as a web-based application. To support the requirements of system criticality, data sensitivity and the need for scalability, a multi-tiered architecture based on the J2EE platform was selected (see Figure 3). The four tiers partition the application so that each tier can be

executed on separate hardware platforms. In addition, several open-source frameworks were adopted to accelerate development times, increase reliability, improve maintainability and promote interoperability of the web application.

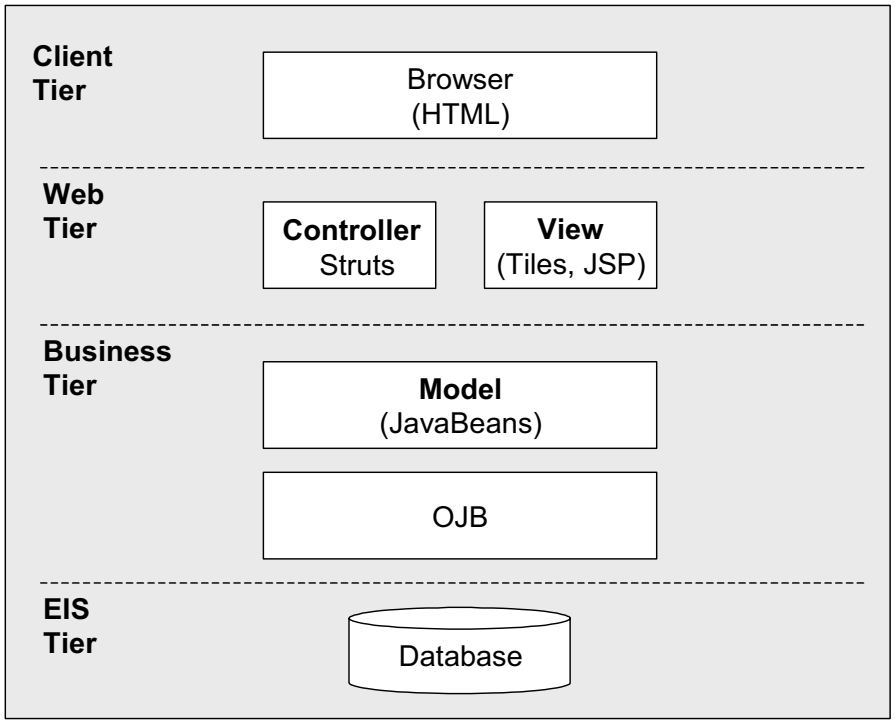

Figure 3: Multi-tiered, J2EE web application architecture.

The core frameworks of the PTMS architecture include the Apache *Struts*, *Tiles*, and *ObJect-relational Bridge* (OJB). Using these open-source frameworks, the development proceeded quickly from prototype to full implementation with minimal additional infrastructure development. Despite continuing changes to the requirements affecting page layout and database design, the impact of these changes were minimized.

The Struts framework drives the application. This framework contains the main Java Servlet that accepts and forwards web requests. Only an XML configuration file is necessary to organize the application flow and set up the page processing. When changes in requirements cause the program flow to change, only updates to the XML configuration file is necessary. With the Struts validation plug-in, a high level of automated form validation with minimal effort was achieved. An XML configuration file is all that is necessary to perform basic form field validations including numeric and date field types and required fields. Alert messages provide extensive feedback to end-users and are part of the Struts validation framework.

The page layout was designed using a Struts plug-in known as Tiles, which allows each page to be broken down into sections. Each page is described in an XML configuration file that specifies which JSP page should be called to fill out each section of a layout. This design allows one template to describe the basic layout, while only sections that change need to be coded as separate Java Server Page (JSP) pages. Therefore, common sections were able to

re-use and the entire layout was able to change by only editing the template. These allowed changes to the entire application page layout be done in a matter of minutes.

For the database interface, an object-relational layer called OJB was used. This layer relies on an XML file to map Java objects to relational database tables and columns. OJB also caches objects in memory to save expensive database calls for data that has already been referenced. Since OJB supports relationships as references and collections, not a single SQL statement was written in the application. All of the database references were written to the objects. The XML mapping file is the only place where table and column names are referenced, so changes to the database only impacted the XML file and the objects. This allowed the rapid development of a working application even while the database was evolving.

4. Data Integration

The integration of disparate data sources from clinical, genomic, proteomic and other data domains will be addressed as the CIMS project progresses into the next phases – the Clinical Study Informatics System and the data integration module. With the dynamic and disparate nature of the clinical and research data, there will be a need to integrate these data sources on an ongoing basis with a federated database approach. This will give users the appearance of a single data source view. These integration processes must be repeatable, flexible and easy to create. Some of these requirements can be addressed using a more efficient and specialized tools that can provide Extract, Transform and Load (ETL), data replication, data synchronization, and data cleansing.

In the PTMS, incorporation of multiple data sources is a one-time load at the beginning of the project. Ongoing data entry into the system will be added via the application interface. This initial data loading can be accomplished using custom scripts or a more reliable tool such as an ETL tool.

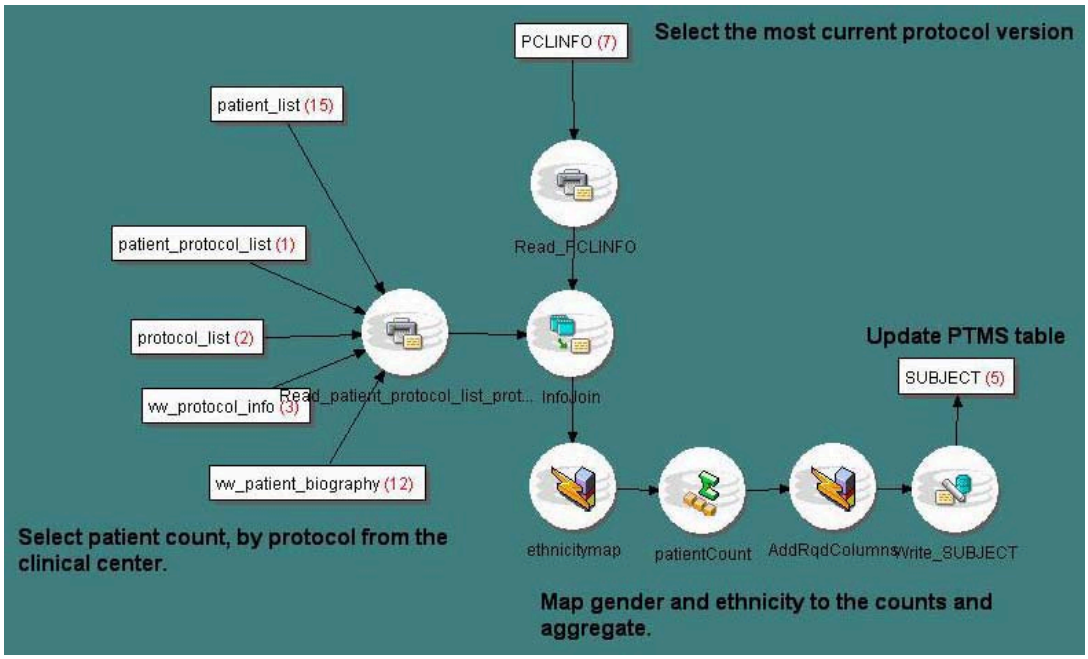

Figure 4: Data flow from legacy sources to PTMS

For the PTMS, an ETL tool from San Francisco-based Embarcadero Technologies called DT/Studio was used to allow users to configure the movement of data from a source system to a target system. Figure 4 shows a data-flow diagram that was visually diagramed and developed for data movement and transformation. It illustrates a subject-count process where patient counts are selected by protocols from the Clinical Center. These counts are then broken out by protocol, gender and ethnicity and used to update the most current version of the protocol in the PTMS.

DT/Studio has allowed the database team to quickly load data from the legacy sources into PTMS. These jobs are modular, allowing reuse of logic so the scripts can be run multiple times with little or no modification. Using the tool, the current and historical data for 300 protocols (including investigator and review information) were loaded within a week of receiving the original data format. In addition, a regularly scheduled process has been created to update patient counts for protocols.

5. Summary

A clinical research system is required to monitor the review process thus facilitating the review of scientific merit of clinical studies. This necessitates a system for tracking and monitoring protocol development. PTMS is a web-based, platform-independent system with a back-end relational database management system. By automating the review process workflow, PTMS can reduce the complexity, improve communication between the investigators and reviewers, and accelerate the review process. The open source, framework-based architecture allows the application to be easily adopted and modified for other research institutions with similar requirements. In addition, the ETL tool enables us to load and synchronize data from multiple data sources.

References

[1] Cavaness, C., "Programming Jakarta Struts", O'Rielly, 2003.

[2] Decker, J., et. al. "Protomechanics: A guide to Preparing and Conduting a Clinical Research Study", Available: http://www.cc.nih.gov/ccc/protomechanics/index.html (2003)

[3] Dumoulin, C., Tiles Project. Available: http://www.lifl.fr/~dumoulin/tiles/, 2003.

[4] Husted, T., "Struts in Action: Building Web Applications with the Leading Java Framework", Manning Publications 2002