

## THE TRIAL BRIDGE™ FRAMEWORK: EXCELLENCE THROUGH INNOVATION

### **Executive Summary**

Before a new drug is made available to patients, it goes through several steps such as: Research and Development, Early Development, Protocol Development, Clinical Trials, FDA Approval, and Post-Marketing Surveillance. It costs between \$800 million to \$1.7 billion and takes an estimated 14 years to get a drug to market with drug patents limited to 20 years (from date of invention). It is estimated that a pharmaceutical company incurs \$0.5 million to \$5 million in foregone drug sales for each extra day a drug lingers in the approval process. These factors, serve as strong incentives for pharmaceutical companies to quickly and accurately complete clinical trials. A primary difficulty in achieving trial completion is that the clinical trials process generates an enormous amount of data which must be tracked, managed, analyzed, and reported to geographically diverse decision makers, investigating physicians, trial sponsors, and regulatory agencies. Managing the sheer volume of data is daunting and time consuming. This process is compounded by the fact that the data is predominantly paper-based and frequently plagued by errors and delays. As a result, the clinical trials process is a costly bottleneck in moving drugs from discovery to market launch.

CTIS, Inc., is a Rockville, M.D.-based health informatics solutions company that has been delivering information outreach, communication and science services, information analysis, decision support, business intelligence services, and research information management, and infrastructure services since 1988. CTIS is an industry leader in producing clinical trial research and management (CTRM) and information technology-based healthcare solutions for our clients worldwide.

CTIS developed the Trial Bridge framework (Trial Bridge) using the knowledge and expertise gained as a major contractor providing comprehensive clinical trials informatics support to the NCI, Serono, and Novartis over a 10-year period. The clinical trials management solution improves the efficiency of the clinical trials process and helps save patient lives by making new drugs available sooner and at a reduced cost. The solution includes a database management system, electronic data capture tools, business intelligence algorithms, role-based access controller, integrated regulatory compliance, and a comprehensive message exchange system. This information technology solution serves as a reliable mechanism to transfer and analyze data between distinct stakeholders: clinical trials sponsors (i.e. pharmaceutical companies, academic medical centers, and contract research organizations), investigator sites, physicians, and governmental regulatory agencies, such as the FDA.

### **Business Challenge**

One of the most significant challenges that researchers face in today's clinical trials environment is the effective and efficient use of clinical information systems to achieve research goals. Collaboration has become a critical and mainstream vector for drug development. Scientists no longer couple all dimensions of the drug development endeavor within the boundaries of a single corporation or research labs. Instead, alliances, partnerships, regulatory oversight, outsourcing, and partnering dominate the life sciences industry. Corporations have become more and more de-centralized and need to be

dynamically reconfigurable. On top of this, the task of drug development has become more and more complicated and the pressure to innovate with speed and reduced cost continues to escalate. In recent years the life sciences industry has witnessed, and in some cases created, an explosion of available information technologies and standards. These offer tremendous potential for improvement in areas such as public safety monitoring, regulatory compliance, organizational productivity, and process quality. All types of life sciences organizations – biotechnology companies, pharmaceutical companies, and health authorities, but also the myriad of related supporting vendors and academic research institutes – are struggling with how best to take advantage of these new technologies and standards. The landscape is complex and getting more so every day. There are many choices, and each possible path is expensive to follow; there is presently no clear pathway to success and longevity in adoption.

Despite the complexity, the utility of standards is widely recognized, and the FDA's Critical Path initiative recognizes the need for increased attention among life sciences constituents in addressing the challenges of interoperability. CTIS' Trial Management Application Framework Trial Bridge is our answer to these challenges from the life sciences industry.

### **Solution Description**

Trial Bridge is a clinical trials research and management applications framework built on proven internet/intranet standards, and a robust relational database technology that puts critical trial information at the user's fingertips. Trial Bridge provides clinical trial development tools needed by investigators, patient care management tools needed by trial administrators, tracking and reporting tools needed by project managers, data entry tools needed at study sites, while maintaining data privacy, security, and accuracy.

Trial Bridge is a CTRM software framework based upon a service-oriented architecture and generic component-based software (internal and third-party), which includes an agile workbench, development tool kit, and support libraries. The framework has an embedded good clinical informatics methodology that includes applicable standards (data standards – MedDRA, ICD, CDE etc., regulatory standards – HIPAA, 21CFR11 etc., clinical standards – ICH-GCP, CDISC, HL7 etc.). In addition, unlike “shrink-wrapped” solutions, Trial Bridge is modified to fit within the client's specific environment and legacy systems. It does not require the client to alter the way trials are run to fit the software's assumptions or parameters.

Trial Bridge utilizes a unique logical or virtual patient record design. The patient data stored within Trial Bridge is logically partitioned and distributed based on the role of the user accessing the information, thereby eliminating the data redundancy and duplication inefficiencies. Simply put, Trial Bridge provides seamless access to clinical trials information and facilitates communication among all key stakeholders conducting a clinical trial.

Trial Bridge framework is represented pictorially in Figure 1 below. The diagram presents the uniqueness offered by the framework, which is interoperability, security, scalability, and robustness without being dependent on any proprietary technology. The framework is also exclusive as its presentation layer can accommodate any browser on any device. The business engine is also independent and can be customized and re-configured to adapt to changing business needs with negligible impact. The business engine also acts as business service, which is designed as per service oriented architecture methodology, implemented by use of web services. The framework thus provides capability to connect to disparate systems or legacy systems with minimal burden. The data layer is also designed such as to

provide connectivity with any leading databases, both open source and proprietary. Thus the framework is designed to provide scalability and accessibility across multiple applications and devices with regards to clinical trials domain.

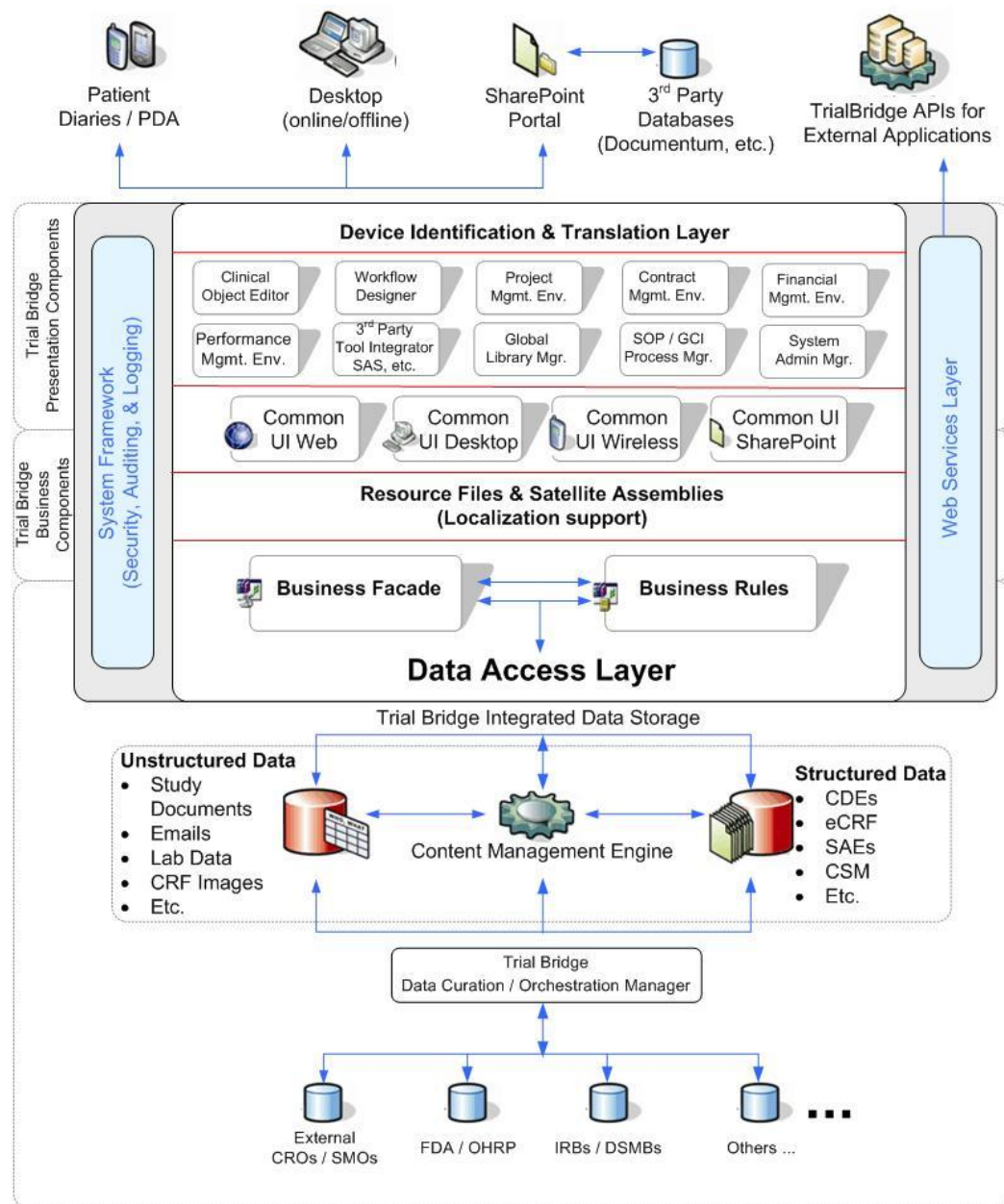


Figure 1 Trial Bridge™ Framework Architecture Diagram

### Solution Benefits

#### *Right Information in Right Hands*

Trial Bridge uses an integrated Role-Based Access System (RBAC) which allows configuration and control of information across multiple users. The RBAC system is designed to simplify user administration procedures by centrally collating the user definitions, access permission assignment and audit trails. This system is designed so that

information exposure is restricted to that needed by the role of user, thus avoiding excess information disclosure. It also results in huge cost savings because administrators are required to manage only one centralized system. The access system is also designed to cater to regulatory compliance needs, such as those mandated by HIPAA.

#### *Any Device, Any Place, Any Time*

Each stakeholder in the drug development process needs to utilize patient data or other trial-related information in their own manner. Nurses or Clinical Research Assistants (CRAs), for example, need information related to administering the drug or the therapy. Investigators or physicians need to access the same data but for scientific and decision support. Healthcare providers need to access the patient data for financial information. Government agencies, such as the FDA, or the trial sponsor need to access the same patient data from the regulatory and research perspective. More often than not, the distinct needs of individual stakeholders, who may not reside at a common location or share computing resources, have resulted in the development of redundant and non-standard data.

#### *Real-Time Reporting of Clinical Data*

Trial Bridge has an integrated reporting engine which empowers business users to perform their own ad-hoc query without any IT support but with IT control. Data analysis can be performed against historical and current data, to evaluate today's performance with yesterdays, thus leading to better decision making with less cost and time. The reporting engine is designed above a common data abstraction layer which insulates reporting applications from changes that occur at the physical layer. Real-time reporting provides systems with capability to be proactive thus providing users with better decision-making capabilities. With reliable and current progress reports, Trial Bridge can be used to provide detailed view of clinical trial progress, forecast expenditures, track actual vs. forecasted, send automated alerts concerning critical data changes or missed deadlines, simulate scenarios, and provide visibility over accrual related information.

#### *Author and Activate New Trials Rapidly*

Trial Bridge maintains a database of information, such as investigator profiles, from all previous trials. This investigator information can be queried and used to add physicians to new trials, avoiding rekeying of information and increasing data accuracy. Combining that information with trial-specific data, such as the Schedule of Events, allows a Trial Bridge client to rapidly define new trials. Once a new trial is defined, study sites selected for the trial can immediately login to that trial and begin the process of accruing patients.

#### *Automated Eligibility Checking for Patient Enrollment*

Trial project managers use Trial Bridge to define an overall enrollment target for a trial, assign individual targets for each study site, and then monitor progress for those targets. Eligibility criteria stored within Trial Bridge for the individual protocol are used to assist site personnel in determining whether a candidate patient qualifies for participation in the trial. Trial Bridge performs data entry error checking in real-time at the study site to reduce data errors and to validate eligibility. Trial Bridge gives sites built-in tools to request "override" permission for individual study candidates.

Trial Bridge has a simple and intuitive interface that gives study sites a consistent and familiar tool for rapidly screening and enrolling patients and automatically makes progress reports available to the trial manager.

### *Track Patient Progress*

Study sites follow the Study Calendar (Schedule of Events tool) integrated in Trial Bridge for scheduling and recording patient visits. Study Calendar is a wizard-based configurable tool that provides the ability to create and edit calendar templates, generate and view prospective calendars of patient activities, track activities as they occur, and manage patient calendar during a study. It also acts as a guiding tool for physicians and/or nurses through each patient visit as per the protocol guidelines. This not only helps in collecting relevant study data but also leads to more accurate Adverse Event coding. Trial Bridge automatically treats visits that fall outside of the specified schedule as Unscheduled Events, unless otherwise authorized by the principal investigator.

### *Rapid and Secure Communications between Trial Participants*

Communication between executive management, trial project management and study sites is simple with Trial Bridge Integrated Message Delivery System (IMDS). IMDS is a self-contained, full-featured e-mail system, built upon Microsoft's Exchange Server that provides reliable message delivery and message confirmation so you know when a message is read. IMDS is accessible only by a trial's authorized participants and eliminates the reliance on faxes and phone calls for daily communications. All messages are permanently stored and audited as part of the trial database for subsequent auditing.

### **Trial Bridge Base Components**

**Case Report Form (CRF) Designer:** CRF Designer is used to create, customize, and manage forms, rules, code lists, and schedule report running time, deploys them to the application server, and set up initial clinical trial accounts.

**Patient Evaluation Manager:** Captures patient's diagnosis and treatment related information as part of the Electronic Medical Record (EMR).

**Patient Registration Manager:** Captures patient's demographic, referring physician, pay or/and emergency information as part of the EMR.

**Protocol Manager:** Includes protocol authoring, trial setup and trial monitoring.

**Adverse Event Manager:** Provides a consistent mechanism for coding adverse events using standard coding dictionaries (e.g. CTCAE, MedDRA, LOINC).

**Treatment Regimen Manager:** Provides a consistent and standard mechanism for treatment courses and dose escalations.

**Message Bus:** is an integration HUB architecture which is based on the Data Integration from various client applications and has the necessary smarts built in to combine data from various formats and present it to the user in a user friendly manner.

**Mobile Component:** Component supports a variety of mobile devices from Mobile OS, WML to HTML-based pocket PCs.

**Security Component:** Ensures compatibility and compliance with HIPAA, CDISC, HL7, ASTM requirements.

### **Trial Bridge Component Library**

**Global Address Component:** Defines attributes and characteristics of organizations and personnel involved in the course of conducting clinical trials and relationships that exist between various people, various organizations, people and organizations, people and documents/clinical trials, and documents/clinical trials and organizations. The component also maintains information regarding different roles an organization or person performs on an organization or in the course of clinical trial.

**Dose Regimen Component:** This component specifies the manner in which patients will be treated on the protocol, what drugs and/or therapies need to be provided to the patients, and the dose schedule. This allows users to define and preset multiple treatment assignments that could be considered as dose levels. This codification allows for electronic transfer of patient and treatment information in a standardized format.

**Site Replication Component (SRCC):** SRCC offers a mechanism for updating captured data across multiple locations. This provides for a scalable solution to the pharmaceutical client. As more trials and users are added to the system, the Trial Bridge server farm can be augmented appropriately.

**Controlled Access to Data Component:** This component provides the ability to meet the confidentiality and blinding requirements of clinical trial data by providing a security layer on top of the final database. The Database Administrator (DBA) assigns access privileges to the final database for the users using a schema of predefined-user roles (CRA, physician, etc.) that the DBA creates in the underlying database.

**Clinical Development Planner Component:** This component permits metadata to be organized, not just at the study level, but also at higher, aggregate levels. The component allows end user to define not only the number of levels of the hierarchy, but also the names to be used for each node. This roll-up effect is used to provide an overview on study status, patient enrollment, percent declared clean, etc., at the various aggregate levels.

**Randomization Decoder Component:** This component offers an interface that the trial sponsor goes through to un-blind a subject during the trial. Pharmaceutical companies typically have official procedures for how un-blinding must be done, in order to preserve the integrity of the trial results. These procedures can include acquiring written approval from upper management or un-blinding committees. The un-blinding interface is driven by the customized workflow a sponsor creates using the clinical workbench and is a series of screens the users work through to complete the un-blinding process.

**CDM and AE Reconciliation Component:** The adverse event reporting or safety reporting tools lie outside of the data collection, clinical data management, and DR phases of the clinical data process. They fulfill regulatory guidelines for the reporting of adverse events, both before New Drug Application (NDA) submission (i.e., during clinical trials), and after NDA approval (so-called post-marketing events). They function by submitting reports of certain types of adverse events within timelines set by the regulatory agencies (e.g., 24 or 72 hours). The reports use standardized forms (3500A, Council for International Organizations of Medical Science, etc.) produced by those regulatory agencies.

## **Summary**

The Trial Bridge framework is unique as it is independent of any proprietary software solution or technology stack. It is designed based on CTIS' wide experience in the CTRM

space and has a proven track record in this field. It is an interoperable framework that can collect or export data in any format, from any device, as per regulatory norms, in a secure manner. CTIS' Trial Bridge framework helps sponsor's tailor, standardize, control, and improve the quality of clinical data. CTIS is a CMMI Level 3 company and this allows us to bring treatments to market more quickly and with a higher level of quality.