CTMS : Vision and Scope - caAERS

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Contents

Change and Review Record

Date	Author(s)	Document Version	Change Reference (Major Changes)
12/06/2006	Warren Kibbe, Northwestern	DRAFT-1	Initial draft scope and vision statement based on Kick-off meeting on 12/6/2006
12/09/2006	Cal Collins, Akaza Research	DRAFT-2	Re-drafted scope and vision
12/12/2006	Ram Chilukuri, SemanticBits	DRAFT-3	Documented short-, medium-, and long-term project goals
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			to the doc for Phase II development
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4/2/2008	Sonja Hamilton	Version 1.0.4	Minor changes and comments throughout
4/3/2008	Robert Morrell	Version 1.0.5	Data Sharing finished (as much as it can be at this time!)
4/9/2008	Jennifer Reed	Version 1.0.6	Updated Phase 2 module definitions and addressed general questions throughout the document. Pulled specific information from the modules into a child document to be used in the creation of use cases and requirement definitions.

Introduction

Purpose of Document

This project charter provides an overview of the caBIG™ cancer Adverse Event Reporting System (caAERS) project. It is a working document to

facilitate communication between NCICBIIT, SAIC, and Booz Allen Hamilton management teams, the caBIG Developer team at SemanticBits, the Adopters of caAERS at Wake Forest, The Mayo Clinic, and CALGB (and any other assigned adopters), the Reporting and Sharing Special Interest Group (SIG), the VCDE and Architecture Mentors, and the members of the Clinical Trials Management System workspace. The document is intended to ensure that the project goals and scope are well defined and well understood by all stakeholders prior to project execution.

Overview

The purpose of this project is to continue the development of caAERS, an adverse event reporting system that is nationally scalable with a robust architecture to meet the needs of the caBIG™ Community. Release 1 of caAERS consists of an application that captures adverse events, uses standardized vocabulary, integrates with local clinical trials databases, and reports to external agencies. The caAERS requirements, data model, and use cases developed during Release 2 will be the foundation for this next phase. The Developer team will execute Elaboration, Construction, and Transition Phase activities for this project. The project will be carried out using the Agile Unified Process Framework, emphasizing continuous integration, testing, and risk management. Three Adopters, WakeForest, The Mayo Clinic, and CALGB, have been assigned and funded by caBIG™ and their input and collaboration throughout this project is critical to the timely release of additional features. SemanticBits will work closely with these Adopters, any additional adopters identified by NCICBIIT, and the Study Conduct Special Interest Group to ensure the deliverables of this project will meet the needs of the caBIG™ Community. The detailed Communications Plan contains additional information on how these communications will be carried out.

The Developer team will continue to develop the cancer Adverse Event Reporting System (caAERS), using a standards-based service oriented architecture and providing tools for integrating data from and to existing clinical and research systems. This project cycle of the cancer Adverse Event Reporting System will provide the following functionality:

- Reporting and change tracking for routine AEs
- Additional Vocabulary integration
- Data Sharing elements
- Internal Routing and Reviewing features
- Increased usability of caAERS
- Additional integration features
- Additional AdEERS functionality
- Additional reporting functionality

Additional Modifications of the Adverse Event Data Capture Tool

The Adverse Event Data Capture Tool is a web-based user interface for manual entry of data surrounding an Adverse Event. Based on information entered through a web interface, the system captures the severity of the adverse event and provides some workflow for identifying and capturing decisions necessary for further reporting. Internal reporting and notification capabilities allow Quality Assurance personnel and/or Clinical Research Associates (or individuals with these roles) to make and follow submissions, review them, and provide methods and interfaces for the Principal Investigator(s) to monitor toxicities. Depending on the priorities identified during the development iterations, it may be necessary to address further reporting requirements such as reporting to cooperative groups, local IRBs, a central IRB, or additional as yet undefined workflows. However, these external reporting requirements will be addressed in the External Agency Reporting module (named Module 4 in caAERS R1). This tool is extensible with a well developed API, enabling integration with data from a clinical trials management system for information about study participants, study coordinators, study PIs, expected adverse events, identity, and security management. We have provided two versions of the application: one that integrates with other tools as part of the CTMS, and a second that acts as a stand-alone, self-persisting version of this tool with minimal functionality to provide some of these capabilities, including entry of basic protocol and participant data, without integration with a more extensive clinical trials management system. The stand-alone system will use common security module (CSM) for identity management and security.

A core focus of the development of this phase is work on the interface and usability. Further work will be done to increase integration with other applications in the CTMS workspace as well as with local CTMSs.

Integration of the Adverse Event Data Capture Tool & Local Clinical Trials Databases

Basic integration into an adopting institution's CTMS has been provided via a standards-based API. This includes both a webservice and caGrid interface, based on the touch points required by the institution.

Additional integration points will be identified during this phase of the project. Further research into the systems (both input and output) that caAERS will integrate with as well as the data types it will work out will be completed, with a

plan developed to address the priority systems. We will continue to work with adopting institutions to meet their needs whether they're working with a local CTMS or caBIG CTMS applications.

The Adverse Event Data Capture Tool interfaces will be able to provide multisystem integration, provided the individual systems are capable of electronic interfaces. Our reference architecture is based on messaging, not static data structures and data exchange, so that this tool can be integrated into multiple systems at individual adopter institutions. We do not consider generating files, even XML files, as meeting the needs of an integrated system. However, it will be possible to export and import data by persisting messages, providing file-based legacy integration should that prove necessary for some of the adopters. We anticipate, however, that each institution will need to be able to provide a single "source of truth" for facts such as studies available, study participants, PIs, data coordinators, and identity services, when those sources exist. Integrating multiple systems for a list of all participants, coordinators, PIs, etc. is outside the scope of this project.

Vocabulary Mapping Service

The reference architecture and data services will utilize the mappings created in other projects and available through the caDSR to facilitate customized reports and forms based on the user's vocabulary preferences. caAERS currently supports CTC 2.0, CTCAE 3.0, and MedDRA 9.0. We will work on including additional versions of MedDRA as well as different vocabularies available through the caDSR including SNOMED CT, NCI Thesaurus, LOINC, HL7 RIM Vocabulary, ICD-9, ICD-O, and others, as identified during the Elaboration phase of this project.

External Agency Reporting

As the APIs and messages necessary for the automated, electronic communication of adverse events (AEs) and serious adverse events (SAEs) among institutions are defined, caAERS will provide interfaces and methods for the messaging of AEs to systems external to the local adopter. We anticipate that this will include two-way communication of adverse events with cooperative groups, national studies, study sponsors, the NCI and the FDA. During Phase I we analyzed the caAERS to AdEERS integration requirements and implemented a subset of them using state of the art SOA principles. During Phase II we will not only complete the caAERS to AdEERS communication but also explore the integration with additional systems. We will also evaluate the interface we instituted for the AdEERS integration and determine if it's usable for other systems.

In some cancer centers that adopt caAERS, it may be the first caBIG™ system in place. The ability of caAERS to provide a persistence model for these adopter institutions will be of paramount importance. Deployed in an environment with the other caBIG™ systems or caBIG™ silver compliant systems, caAERS will provide an extensible framework for adverse event data capture, monitoring, and reporting.

Audience

caAERS is a critical component of the caBIG™ CTMS ecosystem, and a crucial resource for the cancer research community. This includes not only clinical trial administrators and data coordinators, but also the PIs and cancer researchers who are responsible for the safety and efficacy of increasingly complex treatment regimens. The intended audience for this document includes those trialists and researchers as well as the NCICBIIT, CTMS workspace facilitators and project managers at SAIC-F, participants in the CTMS workspace and in the caBIG program in general, and members of the general public who may be interested. We anticipate that the readers may also include biomedical informaticists, software engineers, and cancer registrars.

Related Documents

Listed below are other documents related to the caBIG™ caAERS Project:

- CMTS Patient Study Calendar Vision and Scope
- CTMS caXchange Vision and Scope
- caAERS Development Project Plan
- caAERS Object Model
- caAERS Lessons Learned
- caAERS Software Requirements Specification
- caAERS Requirements Traceability Matrix
- caAERS Risk Matrix
- caAERS Test Approach
- caAERS Architecture Diagram
- caGRID 1.0 design documentation

Terms and Definitions

The following terminology is used throughout this document:

- **Developer** - an organization selected and funded by the NCICB to participate in a specific Workspace to undertake software or solution development activities. For a full list of the responsibilities of a caBIG Developer, see the *caBIG Overview Workspace & Working Group Kick-off*

*Meeting Handbook*distributed in February, 2004.

- **Adopter** - an NCI-designatedCancerCenter selected and funded by the NCICB to undertake formal testing, validation, and application of products or solutions developed by Workspace Developers. For a full list of the responsibilities of a caBIG Adopter, see the *caBIG Overview Workspace & Working Group Kick-off Meeting Handbook* distributed in February, 2004.
- **AEs** - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal investigational) product. NOTE: For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.
- **SAEs**-- Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, or is a congenital anomaly/ birth defect.
- **Routine AE -**
- **Expedited Report -**
- **Clinical Research Associate (CRA)** - Person employed by a sponsor, or by a contract research organization acting on a sponsor's behalf, who monitors the progress of investigator sites participating in a clinical study. At some sites (primarily in academic settings), clinical research coordinators are called CRAs.
- **Clinical Research Coordinator (CRC)** - Person who handles most of the administrative responsibilities of a clinical trial, acts as liaison between investigative site and sponsor, and reviews all data and records before a monitor's visit. Synonyms: trial coordinator, study coordinator, research coordinator, clinical coordinator, research nurse, protocol nurse. Also called Data Coordinator/Manager.
- **QA** - All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with good clinical

practice (GCP) and the applicable regulatory requirement(s).

- **Data Coordinator/Manager** - See Clinical Research Coordinator and Data Management.
- **Data Management** - Tasks associated with the entry, transfer and/or preparation of source data and derived items for entry into a clinical trial database. NOTE: data management could include database creation, data entry, review, coding, data editing, data QC, locking, or archiving; it typically does not include source data capture. This work is often done by a data coordinator/manager or clinical research coordinator. See Clinical Research Coordinator and Data Coordinator/Manager.

Background and Rationale

Background

From Wikipedia, the free encyclopedia:*In cancer treatment, as in other fields in medicine, an adverse effect is an abnormal, harmful, undesired and/or unintended side-effect, although not necessarily unexpected, which is obtained as a result of a therapy or other medical intervention, such as drug/chemotherapy, physical therapy, surgery, medical procedure, use of a medical device, etc. Latrogenesis (literally, generated by a physician) is a common cause of adverse effects, as well as medical error. Using a drug or other medical intervention that is contraindicated may increase the risk of adverse effects. Adverse effects may cause medical complications in the treatment of a disease or procedure and negatively affect its prognosis.*

Adverse events are usually indicated by some result such as morbidity, mortality, alteration in body weight, levels of enzymes, loss of function or as a pathological change detected at the microscopic, macroscopic or physiological level. They may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other chemicals, foods, or procedures (e.g. drug interaction).

The NCI Cancer Therapy Evaluation Program, CTEP, has developed the standard vocabulary for describing adverse events, with the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 in current use (see *http://ctep.info.nih.gov/resources/electronic.html and http://ctep.cancer.gov/reporting/ctc_v30.html* for more information regarding this standard vocabulary and existing tools for managing this vocabulary). The CTCAE includes MedDRA

codes for each CTCAE term and can be organized into a directed acyclic graph (DAG) making it possible to implement standard ontology tools for representing and selecting CTCAE categories, toxicities, and grades. In general, when reporting adverse events, the date of the onset of symptoms, severity (grade) of the event, and duration or end of the symptoms at a specified severity define the reported adverse event episode. However, the reporting requirements can be different, such as for routine AE data collection, study type, and phase.
In addition to onset, duration, and severity, the episode must be associated with an attribution code, which is a determination of whether or not the episode is attributable to the treatment. The allowed attribution codes are:

Attribution Code	**Description**
Unrelated	The AE is clearly NOT related to the intervention
Unlikely	The AE is doubtfully related to the intervention
Possible	The AE may be related to the intervention
Probable	The AE is likely related to the intervention
Definite	The AE is clearly related to the intervention

When reporting adverse events that require expedited reporting, all commercial or therapeutic agents given to the study participant experiencing the adverse event must also be listed. For reporting to CTEP, the NCI should be the sponsor of the study. All serious adverse events should be reported to the FDA, whether part of an IND (Investigational New Drug), trials examining so called 'off label' uses for commercially approved agents, or any serious, unexpected adverse event that is likely to be or clearly related to an agent or device. There are two major types of reports: routine reports and expedited reports, and the reporting requirements vary depending on the sponsor, the type of agent(s) involved in the clinical trial, whether the adverse event was expected or unexpected (as defined in the study protocol), and the severity of the adverse event. Adverse events can be classified into three types: Single episode, where the adverse event occurs, and is not repeated, Persistent, where the adverse event episode continues over multiple

cycles or courses of treatment, and Recurring, where the adverse event episode resolves (the patient has a reduction or abrogation of symptoms), and the same adverse event recurs during a later cycle or course of treatment. More information regarding the interplay of these factors is available at http://ctep.cancer.gov/reporting/newadverse_2006.pdf.

The goal of caAERS is to aid clinical trialists in identifying, monitoring, and reporting adverse events for institutional, cooperative group, NCI sponsored, and industry sponsored clinical trials. The functionality of and the capabilities of caAERS is a critical component to managing the safety and efficacy of complex clinical interventions in the pursuit of more effective treatments for cancer.

Business Justification

The rapid reporting, monitoring and attribution of adverse events is crucial to the safety of cancer patients, and takes on an even more urgent function during phase 1 and phase 2 trials, where the maximum tolerated dosage and efficacy of new therapeutic designs and agents are examined. In designing caAERS, ease of AE reporting and monitoring of patient safety for institutional as well as multisite trials is of utmost importance. caAERS will help support these goals by:

1. Providing a consistent tool for capturing and annotating adverse event episodes. Current tools at the NCI are directed at NCI-sponsored trials.
2. Providing a consistent framework for integration with local infrastructure. Being able to capture and report AEs to PIs and the IRB at a local institution will speed the identification of agents and therapies that need contraindications documented. Currently, there is variable IT support and architecture across cancer centers. Excel spreadsheets and variably designed Access databases are the rule, and make the integration of adverse event data difficult.
3. Eliminating the need to enter one report many times. Entries should only be made once and then electronically communicated to all stakeholders in the reporting process.
4. Enabling mining of collected data to enhance patient safety. For instance, rather than just looking at the precise agents involved in a trial, the mechanism of action of a therapy can be examined and the likelihood of an adverse event for a class of drugs as well the performance/safety of a specific drug compared with other drugs in the same class, as well as identifying classes of drugs that have unexpectedly high rates of adverse reactions.

5. IRB, Consent and Permission procedures, HIPAA and security issues. This represents a serious (and increasingly recognized) security and legal concern for medical centers since CRAs and other personnel involved in the reporting process may inadvertently expose patient identifiers when performing redundant manual tasks like adverse event reporting.

Differences in adverse event reporting tools, the consistency of annotations of adverse events, and most importantly, the lack of electronic communication of adverse events pose a serious barrier in the rapid identification of adverse events at or between institutions. As the combinations of therapies and the strategies for identifying substrata of patients that have varying responses and adverse events to specific interventions become more complex, the ability to electronically aggregate and mine these data becomes increasingly important in the evaluation of the safety and efficacy of new trial designs and therapies.

Modules Defined During caAERS Development

caAERS provides functionality to collect adverse event data, aiding in the identification of the adverse event and the assessment of grade and attribution to treatment. Severe Adverse Events (SAEs) must be immediately reported to the Principal Investigator, and other individuals, key to the management of that trial. In some cases, Routine Adverse Events (AEs) also need to be reported. Expedited reporting to the proper government agencies and to institutional monitoring boards is critical.

The full functionality envisioned for a system to support this process requires multiple modules and areas of development, ad detailed below. Work completed during Phase I of the project is described first, followed by planned work during Phase II, and additional modules that would be beneficial. Adopters can select to employ any or all modules as needed.

Phase I Project Modules

Module 1 - Adverse Events

The Cancer Adverse Event Reporting System (caAERS) has the ability to document, manage, report on, and analyze adverse events (AEs). The system operates as both a repository for capturing and tracking routine and serious AEs and as a tool for preparing and submitting

	expedited AE reports to regulatory agencies. It can be deployed as a stand-alone application or as an integrated module within the caBIG Clinical Trials Suite (CCTS). **Module 1a - Adverse Event Capture** caAERS works with cancer prevention and therapeutic trials and can accommodate a range of intervention types, including investigational and commercial agents, radiation, surgery, and medical devices. Adverse events can be coded in caAERS using either CTCAE or MedDRA. Users can now enter Adverse Event information, prepare and submit report, configure AE notification rules, and search adverse events in the system. Currently, multiple pieces of information can be imported from existing CTMS interfaces, such as patient and protocol-related AE information (patient information, study information, investigators, etc). However, some instances of caAERS require direct entry since there is not a local CTMS or it is unavailable for integration. **Module 1b - Studies** caAERS has the ability to capture study information. This information can be imported from a local CTMS, captured automatically (basic details) from C3PR when using caAERS as part of the CCTS, or entered manually using the caAERS web interface. In addition to capturing the protocol information (diseases, therapies, agents, and treatment assignments), caAERS also tracks what personnel (research associates, investigators, etc) are associated to the study, the study's sponsors, sites, and identifiers. **Module 1c - Subjects** Subjects that are participating in studies can be managed in caAERS. caAERS has the ability to capture general subject information, what study(s) they are involved in, and their AE history. Subject information can be imported from a local CTMS in a batch, captured automatically (basic details) from C3PR when using caAERS as part of the CCTS, or entered manually using the caAERS web interface. As a patient's involvement in a study changes, it is easy to add the association to that study. **Module 1d - Rules** The caAERS system features a powerful, state-of-the-art rules engine, which can capture a range of sponsor, institution, and protocol-level reporting requirements.Using these rules, caAERS can automatically determine if an adverse event requires expedited reporting and when and to whom the report must be submitted -- for any of an organization's trials.

The business rules used by caAERS can be authored within the application itself or imported from a library of approved rule sets. The rules can also be exported for use outside of caAERS. The rules determine appropriate notification action (reports required) based on multiple properties such as AE category, AE term, AE grade, protocol, sponsor, hospitalization/ hospitalization time, expectedness, attribution, reporting time/period, and trial phase.

caAERS also includes is an easy-to-use report template generator, which allows users to build and customize reports. As part of this report generator, there's an advanced email-based alert system that can be customized along a number of dimensions (message content, recipients, delivery times) to ensure that notifications and reminders are sent out as needed. In addition, to help organizations stay in compliance with AE reporting regulations, the caAERS application comes loaded with a full complement of industry-standard AE reports, including the FDA MedWatch 3500A form, the CTEP AdEERS reports, the NCI-DCP SAE form, and CIOMS.

Module 1e - Administration

caAERS can be a completely self contained system. It has custom configuration to work with CTMS if desired, a separate password policy for users, and the ability to create and manage research staff (users of caAERS), including different levels of access. Separately, Organizations and Investigators, which are required for Study creation and AE tracking, can be imported or manually added into caAERS, with the majority of the organizations included in the default installation. There's also the ability to import MedDRA, to support Module 3.

Module 2 - Interface Between AE Capture Tool & Local Clinical Trials Databases

Module 2 facilitates communication between the database created in Module 1 and the participating institution's clinical trials (CT) database. caAERS has the ability to interface with local clinical trial databases to increase efficiency and reduce duplicate data entry. This allows the following capabilities:

- Acquisition of protocol and study participant data by caAERS from local systems.
- Export of related patient, protocol, and AE information from caAERS into local CT Databases and other CTMS application components for aggregation and analysis.
- AE data submission and exchange of ***prospective*** adverse event information between caAERS and local trial data

management systems or electronic data capture (EDC) systems.

These capabilities require standardizing vocabularies and data elements between caAERS and local systems. This process is driven by the caBIG VCDE harmonization work that is done with the caAERS system and supplemented by mapping of caAERS data elements to the equivalent data elements in the local system as defined in Module 3.

Capability (1), acquisition of protocol and study participant data, is well-defined in the caAERS R1 use cases; our reference implementation scenario allows for the provision of published APIs to facilitate message-based data exchange in application modules. The system should support bi-directional data transfer. It should also support an acknowledgement of submissions by providing a message back to the local systems that is computable by the local system providing either a success or failure of transmission indicator. Our implementation will be based on SOA and will leverage the enterprise service bus (ESB) implementation called Apache ServiceMix. We will also leverage a variety of enterprise integration patterns such as message broker and message adapter in our implementation. Reliable messaging will be implemented. Capability (2) is less specific but will require further analysis of local CTMS capabilities and will be discussed with stakeholders as part of the Elaboration Phase. Capability (3) is a prospective functionality not closely addressed in the current caAERS R1 use cases but that may be desirable. The team will proceed with further definition and development pending discussion with stakeholders and analysis of local CTMS/EDC capabilities.

Module 3 - Vocabulary Mapping Service

Module 3 utilizes mappings created in the CTMS Metadata/Vocabulary project to support customized reports and forms. The initial build of caAERS encompasses only the CTC - MedDRA mapping necessary to support searching on AE category and term during data capture and for reporting (CTC 2.0, CTCAE 3.0, and MedDRA 9.0). This will also include mechanisms to access/edit mappings of codes and support future CTC Coding versions.
Mapping of other vocabularies has been deemed a low priority and not needed to meet core functionality. Therefore, a high level mapping using SNOMED and LOINC will be addressed later as part of the development of Module 8 (Assistance in Grading of Qualitative AEs).

Module 4 - External Agency Reporting

Module 4 expands the functionality of Module 1 to electronically communicate SAEs to AdEERS.

Based on the rules created, it's possible an SAE may need to be sent to AdEERS. If this is the case, caAERS has the ability to subit a completed report to AdEERS.

Module 13 - Security

caAERS has been set up to work with an institutions existing security framework. If an institution already has user accounts in place, caAERS can be integrated into the existing system so users only have one user name and password.

Access to the information in caAERS is also controlled. The different Research Staff roles limits the information that can be accessed by each user. These controls are handled in the Administration Module (Module 1e).

Phase II Project Modules (designed to be addressed in this project)

Module 1 - Adverse Event Data Capture

Phase II will enhance the work done during Phase I, with the Developer's addressing the adopter's and elaborators needs while increasing the usability of caAERS. Additional data entry activities will be automated/received from interaction with the CTMS interface (Module 2).

Module 1a - Adverse Event Capture

caAERS currently allows the tracking of Routine AEs. The Developer will work with the elaborators and adopters to identify additional use cases and requirements to enhance the tracking, handling, and reporting of Routine AEs. We will also work to identify additional elements that can be captured \automated using the CTMS interface and other tools.

To support Module 3, the Developers will implement the use of a selection of additional vocabularies.

Module 1b - Studies

The Developers will continue to ensure integration with CTMS components at instutions, and provide APIs that pull study data from the CTMS. In addition, the Developers will work with the adopters and elaborators to identify additional requirements for study creation, such as the creation of study-specific fields and instructions.

Module 1c - Subjects

The Developers will ensure existing features continue to work for all adopters and elaborators. In addition, they'll work with the elaborators and adopters to determine additional reporting needs for subjects.

Module 1d - Rules

The Developers will work with the adopters and elaborators to identify additional use cases and requirements around RuleSets and rule creation. Areas that will be explored include rules specific to patients, research staff roles, institutions, and attributes.

Module 1e - Administration

The Administration Module of caAERS allows users to setup the system, creating application users (research staff), investigators to be associated with studies, organizations, importing data (studies, subjects, routine AEs, etc), and setting it up to allow email and communication with other systems.

As caAERS is adopted by more groups, different ways of handling security, studies, and information are being introduced. The Developers will work with elaborators and adopters to identify any additional use cases involving the administration of caAERS, such as adding more control over the import features. The research staff roles and responsibilities will also be reviewed to identify additional needs based on the adopter's different methodologies (supports Module 13).

Module 2 - Interface Between AE Capture Tool & Local Clinical Trials Databases

Phase I identified some integration requirements and setup some initial integration, but additional work will be done during Phase II to facilitate communication between the caAERS database and an institution's clinical trials (CT) database. A more comprehensive list of systems (input and output) will be identified, as well as different data types that caAERS needs to work with. There are existing APIs which may be expanded. Further identification and integration will allow the following capabilities:

1. Acquisition of protocol and study participant data by caAERS from local systems.
2. Export of related patient, protocol, and AE information from caAERS into local CT Databases and other CTMS application components for aggregation and analysis.

(Currently only the AE report can be exported.)
3. AE data submission and exchange of ***prospective*** adverse event information between caAERS and local trial data management systems or electronic data capture (EDC) systems.

Capability (1), acquisition of protocol and study participant data, is well-defined in the caAERS R1 use cases; our reference implementation scenario allows for the provision of published APIs to facilitate message-based data exchange in application modules. The system should support bi-directional data transfer. It should also support an acknowledgement of submissions by providing a message back to the local systems that is computable by the local system providing either a success or failure of transmission indicator. Our implementation will be based on Service Oriented Architecture (SOA) and will leverage the ESB implementation called ServiceMix. We will also leverage a variety of enterprise integration patterns such as message broker and message adapter in our implementation.

Capability (2) is less specific but will require further analysis of local CTMS capabilities and will be discussed with stakeholders as part of the Elaboration Phase.

Capability (3) is a prospectiveWiki Markup functionality not closely addressed in the current caAERS R1 use cases but that may be desirable. The team will proceed with further definition and development pending discussion with stakeholders and analysis of local CTMS/EDC capabilities.

Module 3 - Vocabulary Mapping Service

In Phase II the Developer will add the support of the new MedDRA vocabulary, and explore the possibilities of supporting addition vocabularies. However, mapping of other vocabularies has been deemed a low priority and not needed to meet core functionality. Therefore, a high level mapping using SNOMED and LOINC will be addressed later as part of the development of Module 8 (Assistance in Grading of Qualitative AEs).

Module 4 - External Agency Reporting

During Phase I, the Developers enabled caAERS to submit SAEs electronically to AdEERS. During Phase II, the Deveopers will complete the caAERS to AdEERS electronic communication. The Developers will also look to further reporting by supporting electronic communication of SAEs to other participating entities/systems and providing generic alert messages to national cooperative

groups and industrial sponsors involved with NCI funded protocols.

NOTE: Full CDUS requirements are not within scope of this project.

Module 5 - Internal (institutional) Routing and Review

Module 5 provides a standardized electronic routing mechanism to alert institutional monitoring groups such as the Data Safety and Monitoring Board (DSMB) and Institutional Review Board (IRB) to adverse events. The Developers will analyze what level of internal routing and review needs to be instituted. It is foreseeable that there will be two types of routing required, one from a group perspective and one from a site perspective.

Workflow and ownership transition flexibility will be important to accommodate different operating environments (actors and linkages will be different across institutions and within institutions across time).

Module 12 - Automated Decision Support for Expectedness of AEs

This module refines the capture of adverse events data by providing protocol-specific information against which the event is compared. This enables the system to determine whether an adverse event is expected or unexpected at the initial point of entry. The Developers will work with the adopters and elaborators (including CTEP) to identify the specific use cases around expectedness of AEs to determine what information needs to be collected and how caAERS will handle the information (or the absence of that information).

Module 13 - Security

As more elaborators are brought on, more systems and security measures are introduced. The Developers will review current integration methods, and expand them as necessary to ensure users only need to have one user name and password. In addition, the Developers will revisit the current requirements for the user roles, which limit access to modules and data. Where necessary, they will create additional roles and/or expanding the restrictions on existing roles.

Data Sharing

Data sharing refers to exposure of data for analysis outside of the sponsor's initial analytical activities. Data sharing will be driven by three imperatives:

- The overarching goal of caBIG to enable sharing of published data in a semantically interoperable fashion.
- The emerging legal requirement of the new FDA data sharing law.
- The need for authoritative bodies in multicenter trials to aggregate and analyze AE data.

These three goals will intersect to a very large extent, but with different timelines, security restrictions, and analytical needs. The key variables to understanding data sharing restrictions are the pre- and post- publication intellectual property concerns, and the constant HIPAA restrictions.

The Developers will work with the Adopters and NCI to determine the best model to be used, understanding the fluidity of the environment as the legal requirements of the new law are detailed, and various regulatory bodies react to them. There will be two levels of requirements, an overarching set which spans all groups, and additional requirements per each individual site's requirements. NCI is currently performing an analysis of requirements based on the new law, and will be a good starting resource.

Code Base Refactoring

During Phase II, the Developers will be participating in a CTMS-wide code base refactoring project. All applications in the CTMS will be evaluating the services they provide to determine what redundancy exists and what application the service should belong too (who will be responsible for maintaining it). Once the decisions are made, the Developers will be involved in a recoding effort to remove the redundancy and increase the efficiency of caAERS.

Enterprise AE Analysis

There have been discussions about caAERS acting as the central ASE Reporting System for receiving and processing SAE reports on behalf of CTEP, DCP, and possibly other NCI divisions and programs that sponsor clinical trials. This could include replacing AdEERS with caAERS. Working with NCI-designated Subject Matter Experts, the Developers will perform a review and analysis of NCI's needs for the proposed Enterprise AE system. This will result in a detailed gap analysis between their requirements and the current version of caAERS, and may also affect development efforts.

While this effort occurs, the Developers will continue to refine communications with AdEERS and other systems, per Module 4.

Modules Out of Scope for this Project (defined for future development)

Module 6 - Integrated Repository of AE Data

Module 6 establishes a data warehouse for evaluating adverse events across protocols, sites, a network, the nation, ect. This repository sets the stage for later modules that provide information for data mining and public safety communications.

Module 7 - Acquisition of Lab Data to Quantitatively Identify Adverse Events

Module 7 will assist in the grading of quantitatively identified adverse events found in lab data acquired from local laboratory systems. Grading will be based on CTEP's CTC version 2.0 and CTCAE version 3.0. An application called caLoegs is currently being developed by City of Hope that addresses this module. Once the application is completed, we will review the possibility of integrating with it.

Module 8 - Assistance in Grading Qualitative Adverse Events

Module 8 will provide assistance in the grading of adverse events found through clinical observation. Grading will be based on CTEP's CTC version 2.0 and CTCAE version 3.0. It may be feasible to display the different grades available to assist the users in choosing the correct one.

Module 9 - Study Participant Self-Reporting of Adverse Events

Module 9 facilitates the reporting of adverse events by the study participant and their family caregivers. Data will be collected via web-entry or via a telephone.

Module 10 - Data Mining for Risk Patterns

Module 10 enables authorized individuals to gain access to the Adverse Events Data Warehouse for data mining across protocols. Information collected for the current CDUS system is also accessible. Statistical analysis of risk patterns should provide opportunities for improved clinical trials and knowledge acquisition.

Module 11 - Public Safety Website

Module 11 addresses dissemination of information about adverse events and drug and procedural safety alerts to the public. It uses the information collected in the data warehouse and evaluated via the functionality in the previous module.

Related Projects

- **caDSR** - Cancer Data Standards Repository
- **caTIES** - Cancer Text Information Extraction System, which automatically provides partial annotation of surgical pathology reports (see Appendix A)
- **caTISSUE Core** - caTISSUE's core solution for biospecimen inventory, tracking, and basic annotation that may be used by biospecimen resource facilities (see Appendix A)
- **CTMS Workspace projects** - CTMS workspace project development will be driven by caSPR, the cancer Structured Protocol Representation model shared by caBIG, CDISC, and HL7.
- **ICR Workspace projects**- sample-based research data and analytical and genomic/ proteomic annotation tools

Project Dependencies

The success of the project is predicated on timely and successful interaction of the Developer Team with the Adopters, the SIG, the VCDE and Architecture Mentors, the CTMS workspace and with the NCICBIIT and caBIG™ and NCICBIIT tools as follows:

1. Review of draft artifacts by the members of the workspace and NCI will be timely and thorough.
2. Solution must meet the legal requirements around Data Sharing.
3. At least two adopters will be willing and able to implement and test the system at their institution according to the development timeline. The developers will have access to the required subject matter experts and clinical trials team members at the adopters sites through weekly teleconferences, as well as periodic face to face meetings.
4. The Common Security Module (CSM) tool provided by the NCICBIIT must support levels of user authentication and authorization that are required by the security and privacy policies at the Adopter sites.
5. Using CSM, each CTMS mdoule must be able to implement recognition of a user and

management of the user's authorization privileges across applications.
6. Technical support for CSM, caCore, and other NCICBIIT-mandated tools successfully resolves all problems in a timely way.
7. Support from the EVS and caDSR teams for adding vocabulary, running the Semantic Connector and UML Loader, and resolving model and vocabulary questions will be timely and knowledgeable.
8. The goal of all software development is silver-level caBIG-compatibility, as defined by the caBIG Compatibility Guidelines that are current at the time of system design.

Risks and Key Challenges

A number of critical challenges will be faced by the Developer in this project. To maximize the success of the project, we have worked to identify a number of these challenges before project initiation and consider how they may be addressed. This preparation combined with active stakeholder involvement and risk management throughout the course of the project provides a compelling strategy for success. The challenges faced include:

- **Object Model Consensus** - Consensus on object models that adequately support all agreed upon use cases. At this point in time we believe that the Release 1 models adequately reflect the use cases, although the models incorporate a lot of exception handling that may not be identified as priorities for the Adopters in this project.
- **Object Model Recoding** - The refactoring of the code across the CTMS workspace could increase the workload for the Developers and require additional configuration by the adopters.
- **Adopter Practices** - Approval of Adopters' IRBs to allow incorporation of the software into their environments, if required. Another challenge is being able to address each adopter's requirements/models for capturing AE information without negatively impacting the other Adopters' workflows. Also, it's important that the Developers ensure the adopters and elaborators use caAERS terminology the same way; for example, all parties need to agree on the definition of a routine adverse event.
- **caBIG Standards** - User resistance to annotating according to caBIG standards rather than according to procedures and systems they are used to.

- **Demonstrating local CTMS integration and capturing protocol, study participant (SP), and treatment information from the CTMS** - A key goal is to enable local CTMS integration to trigger AE "stub" generation, as well as provide AE report data back to the CTMS for analysis/reporting. Key caBIG & external standards and modules are being developed to enable this level of integration, particularly the Clinical Trials Object Model (CTOM), CDISC ODM, and the Trial Design Model (TDM). These standards, plus more general Silver compatibility guidelines, will enable integration with CTMS databases and modules such as C3D, OpenClinica, Protocol Lifecycle Tracking module, Patient Study Calendar, and Lab Hub. To make caAERS useful to the widest number of cancer researchers in a timely manner, there may also be a need to support integration with legacy systems that are not yet caBIG compliant. We will explore this issue with Adopters and stakeholders to determine what other modes of integration (CSV, SQL load) are needed and whether they are a priority for the caBIG community as a whole.
- **Triggers and Notifications** - When a suspected or known adverse event is captured, a set of notifications and reports must be initiated based on the particular requirements of the protocol, institution, sponsor, and regulatory agencies involved with the AE. For example, all AEs of grade 4 and above for Phase II trials may require a notification to the study chair and a report to the sponsor once the study chair has confirmed the SAE. In another example, a CTEP-sponsored trial may require distinction between a "Persistent AE", one that extends continuously, without resolution between treatment cycles/courses, and a "Recurring AE", one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course. In this case, initial submission of the AE as a routine CDUS report and expedited AdEERS will be determined based on the CTC grade of the AE, and subsequent submission of the event will be based on its categorization as recurring or persisting and whether it increases in seriousness.
  We propose to use a rules engine that is flexible yet easily configurable to enable a wide variety of behavior. Event actions should be atomic and reusable in different combinations to make up the triggers needed to satisfy these diverse requirements. This architecture will allow the system to work for a wide array of organizational types and business process flows. To expedite implementation, the system will include default and template

rules for common notification requirements, while allowing users the ability to derive new rules from these templates or create their own from scratch.

- **Vocabulary mapping** - Development of tools for vocabulary and coding system mapping will need to meet current requirements for support of CTC 2.0, CTCAE 3.0, and MedDRA terminologies as well as enable support for additional terminologies in the future, such as the forthcoming revision of the CTC currently under development at NCI. The system will provide functionality to update/maintain the core terminologies and their mappings to each other in a way that enables local configuration by caAERS adopters while ensuring consistency across centers. Meanwhile the system architecture must provide logical structures to enable major terminology upgrades and additions in the future.
  To achieve these goals, the Vocabulary Mapping module will support an extensible terminology and mapping architecture with interfaces for authorized users to update and add to the core terminologies/mappings.

- **Integrating sponsors and regulatory agency stakeholders to capture requirements** - Incorporating capabilities to integrate with and report to external agencies and organizations, either sponsors or regulatory bodies such as FDA, will require articulation of the requirements of those external bodies. Much of this information will be accessible in existing specifications for creating and formatting AE and SAE reporting (such as CTEP/AdEERS guidelines available on the web at http://ctep.cancer.gov/reporting/adeers.html). We also expect the Adopters, and where relevant, NCICB to provide knowledge of these requirements and access to appropriate stakeholders. We will contact agencies directly when necessary to further clarify requirements. Meeting this challenge will be critical in both the requirements gathering and testing activities.

Project Constraints

The project will be conducted under the following constraints:

- The priorities of the members of the Reporting and Sharing and Study Conduct SIGs, and the shared vision of what is needed, continue to evolve as we all learn more about caBIG, about the activities of other workspaces, and about the goals and needs of other cancer centers. We

will address this by soliciting review of all documentation and CDEs by the other developers, the Architecture workspace, and the VCDE workspace.

- The software is required to be caBIG-compatible at the silver level.
- The project team is required to use the Common Security Module (CSM) provided by the NCICBIIT for user authentication and authorization.

Critical Success Factors

The following are critical success factors for the project:

- Timely and active participation of representatives of all groups identified in the Audience section above in deliverable review, requirements determination, and usability testing
- Availability of necessary resources, personnel and equipment at both developer and adopter sites. This depends both on resources approved by the NCI and on our ability to rapidly engage staff with the required skill sets (See Risks and Key Challenges above)
- Tight coordination of the three development projects currently in the CTMS workspace, and coordination with any additional funded efforts as required
- Timely, skilled support for use of caBIG tools like caDSR and the caGRID software
- Timely feedback on deliverables
- Cooperation of Adopters, other resources, and program management to keep the project on schedule.

Links and References

- CTEP Adverse Event Expedited Reporting System (AdEERS) http://ctep.cancer.gov/reporting/adeers.html
- CTEP, NCI reporting guidelines: http://ctep.cancer.gov/reporting/newadverse_2006.pdf
- CTEP electronic applications: http://ctep.cancer.gov/resources/electronic.html
- CTEP Resources: http://ctep.cancer.gov/resources/

	• Patient Safety Network at http://psnet.ahrq.gov/ A government sponsored site with a glossary and articles on all kinds of threats to patient safety, including adverse effects, drug reactions, medical error, iatrogenesis, etc. • Medical Product Safety Information: MedWatch. http://www.fda.gov/medwatch/safety.htm The primary public site for listing safety alerts for drugs, biologics, devices and dietary supplements, recalls, market withdrawals, public health advisories, links to the VAERS and MAUDE databases, etc. Maintained by the FDA