Clinical-Trial Breakout Session

Boston Guideline-Sharing Workshop (March 3-4, 2000)

Participants: Attendance: Samson Tu, Mark Musen, Doug Bell (UCLA), Sam Wang (Partners IS), Jeremy Wyatt (University College of London), Mario Stefanelli (Pavia), Doug Fridsma (Stanford), Felipe Atenza (DSG), Judith Douglas (FCG), John Silva late attendance

Facilitators: Alexa McCray , Carol Broverman, Scribe: Samson Tu

Abstract (Samson Tu)

The clinical trial breakout session (1) discussed how clinical trial protocols differ from practice guidelines, (2) examined the life-cycle of creating, conducting, and analyzing clinical trials, and (3) described various tasks associated with phases of the life cycle, and (4) proposed a few small steps that we can take in the immediate future.

We agreed that guidelines and clinical protocols share many common elements that vary in degree of importance (decision-making, temporal issues). With a few exceptions (such as grading of evidence needed in describing guidelines), most modeling constructs required in representing guidelines are always needed in representing protocols. However, because clinical trial protocols are scientific experiments whose conducts are heavily regulated, decision support for management of patients is only a small part of a range of possibilities in providing computer-based support for uses of clinical trials.

Explicit specification of tasks involved in different phases of a clinical protocol's life cycle is a prerequisite of understanding representation requirements of modeling clinical trial protocols. The knowledge required for analyzing statistical soundness of a trial design or trial results is very different from those needed for recommending appropriate dose changes when a patient is experiencing drug-related toxicity.

An enumeration of tasks involved in designing, conducting, and analyzing clinical trials suggests that there is a research agenda that cannot be carried out without participation from a large number of stake holders. A single project can only work on one aspect of a much larger problem. I believe that the implication for Intermed is that we need to (1) specify carefully the tasks in the life cycle of clinical trials that we want to support, (2) recognize that the model we develop is necessarily partial, and (3) collaborate with other groups to harmonize our respective models.

Summary (Based on Carol Broverman's Presentations)

1. Distinguishing Characteristics: Clinical Trials (CT) versus Guidelines

- Strong scientific design
- Complex visit, intra-visit-tasks, inter-visit tasks sched.
- Randomization (patients, providers, hospitals)
- Data gathering critical; requirements are regulated
- Workflow compliance is regulated
- Strict eligibility criteria. Eligibility criteria only hold until enrollment; separate from any "applicability criteria" that must hold at other points in lifecycle
- More prescriptive nature
- Pre-anticipated workflow deviations and pre-defined exception handling mechanisms
- Cycles, subguidelines, iteration, looping, retries, delays (especially in oncology)
- More granular detail
- Revisions/amendments/versioning are a given
- Double-blind studies impose requirements on "exposure" of protocol detail

- Different views: sponsor, site, patient
  - Clinical trial registries that are aimed at patients
  - Instructions to subjects who are on-study
- Coordination intra-site and inter-organization
- Sponsor oversight/monitoring of performance of sites (especially industry)
- Interim analyses required during lifetime of study

2. Clinical Trials Lifecycle

- Identified Clinical Trial Lifecycle stages with different tasks and requirements
- Trial inception (an idea)
- Trial design
- Trial conduct/execution
- Trial data collection (sometimes separate)
- Trial data analysis
- Trial findings feed into new trial ideas/designs
- Trial data meta-analysis

3. Task-Driven Requirements

A representation is not self-proclaiming. Applications and tasks will determine representation requirements Approach taken at the breakout session was to enumerate tasks per life-cycle stage.

3.1 Tasks during trial design

- Formulation of trial, documentation of sources
- Statistical validation (power calculation)
- Eligibility criteria specification
- Accrual simulation
- Ethical review/IRB (track communication)

3.2 Tasks during trial authoring

- Authoring is a "supplier" to different applications/users
- Analysis of user base and user goals required
- Logical model to support authoring needed
- Needs to be intuitive to clinician/knowledge engineer but must be able to capture what is needed in level B and C
- Mapping between different models needed (level A-C)
- Trial documentation exchange/reuse of text
- Trial monitoring/compliance
- Trial data collection

3.3 Tasks during trial accrual

- Matching a patient to a set of trials
- Matching a trial to set of eligible patients
- Formal eligibility determination
- After Informed Consent obtained
- Connectivity to an electronic patient record and ancillary systems (e.g.; lab, radiology) is an implied prerequisite for precision

3.4 Tasks during trial conduct/execution

- Monitoring visit workflow of individual patients on trial
- Monitor visit/tasks of individual patients on trial
- Support/Monitor data collection of individual trial

- Inter-visit tasks and reminders
- Generate CRFs (Case Report Forms)
- Aggregate trial management within a site (CC/site)
- Aggregate trial management across sites (CRA/sponsor)
- Adverse event monitoring/reporting
- Resource management
- Communication/coordination (intrasite, site to sponsor)
- Monitoring visit workflow of individual patients on trial
- Support/Monitor data collection of individual trial (CRF)
- Inter-visit tasks and reminders
- Aggregate trial management within/across site(s)
- Adverse event management/monitoring/reporting
- Resource management
- Communication/coordination (intrasite, site to sponsor)

3.5 Tasks during trial data analysis (deferred)

3.6 Tasks during trial meta-analysis (deferred)

3.7 Additional Considerations

- Requirements must consider other different trial designs besides randomized trials such as prospective cohort and multi-arm cross-over
- Consider requirements of trials per different disease/treatment areas (E.g.; cycles are idiosyncratic to oncology)

4. Going Forward

4.1 More Detailed Requirements

Further refinement to requirements in functional areas would come from task detailing per life-cycle stage. These functional requirements would shed light on representation requirements and infrastructure requirements.

- Further work on functional requirements (eg.; what is the complete set of tasks, and how to prioritize them?)
- Some special representation needs?
  - E.g.; data collection visits and CRFs
  - Time windows for protocol visits/tasks
  - Uncertainty
- What special infrastructure requirements?
  - Authoring tool requirements
  - Dissemination of amendments
  - Versioning control/maintenance

4.2 Problems/Tasks

- Identify users/stakeholders
- Expectations and requirements; solicit input
- Evaluate existing standards and requirements for protocol content and reporting
- Evaluate and extend existing representation(s)
- Create research/consortium testbed
  - E.g. Protocols authored in “standard” representation, sample test patient data….
  - Build demonstration systems that use testbed
- Promote shareability and collaboration

4.3 Plan and People

Problem of getting resources, money and time to work on these tasks, when everyone is already committed to their projects.

Concrete tasks for this group:

- CT-specific discussion list (Lucila Ohno-Machado)
- CT-specific web-site (Lucila Ohno-Machado)
- AMIA panel participation (Carol Broverman)
- White paper(s) describing research agenda
    - Jeremy Wyatt to take initial lead, solicit input from workshop CT participants
    - Aimed at informatics and clinical trials audiences