Considerations for modeling clinical-trial protocols

In contrast to guidelines that assist clinicians in *decision-making*, clinical-trial protocols emphasize the *work-flow* aspect of patient management. They specify the sequencing and repetition of interventions that are the subject of the clinical experiment, enumerate the studies that need to done on a regular basis, and define algorithms for adjusting interventions based on reactions to previous interventions. In the past, I had primarily worked with phase 3 cancer and HIV clinical-trial protocols. The GLIF modeling constructs developed so far should be applicable to the algorithmic modeling requirements of clinical protocols. Additional issues I encountered include:

1. Often protocols are not explicit about how work is divided into visits. A chemotherapy may talk about "day 1" and "day 8" treatment, and one can assume that each map into discrete encounters. However, it is not always so clear. For example, a protocol may specify what need to be done on consecutive days, and, without additional background information, it may not be clear whether these tasks (1) can be done by patients at home, (2) requires daily visit to the clinic, or (3) require in-patient stays.

2. Cancer protocols often have intrinsic timelines that is different from calendar timeline. "Day 8" in a chemotherapy may not be the 8th calendar day after the start of a chemotherapy, if, for example, treatment needs to be delayed because of toxicity. In ONCOCIN, for example, we abstracted from calendar times and talked in terms of "cycles" and "subcycles." "Day 1" and "Day 8" were modeled as two subcycles of a chemotherapy cycle.

3. A clinical trial may be doubly blinded. An advise system that provides decision support to clinicians can't know the arm to which a patient is randomized. Such protocols need to be modeled without regard to randomization. Thus, a protocol document may describe 2 arms of treatment, but a model of the protocol should have only one branch, because the execution system won't know the arm to which a patient is assigned.

4. Cancer clinical trials have well defined grading system for toxicities. These require mechanisms for making abstractions from observations into toxicity episodes. Yuval Shahar's Resume system is precisely designed for this kind of abstraction task.

5. Clinical trials adjust management of patients based on their reactions to previously administered treatment. Thus, you need a rich language for making temporal queries. These queries depend on temporal context, require ordinal selection, and need to make temporal comparisons. Michael Kahn's TNET did the job for ONCOCIN. Amar Das developed Chronus for T-Helper, and the current EON system has a Chronus-II query system.

6. The most complicated part of a drug protocol may be the part that describe how to adjust treatment based on toxicities. In cancer and AIDS protocols that I have dealt with before, these treatment modifications are often organized by classes of toxicities. Often authors don't specify *interactions* among possible toxicities. There can be two kinds of conflicts. First, there can be more than one dose attenuation requuirements. In most cases, our clinical collaborators told us to take the minimum of the doses as adjusted for different toxicities. However, on a few occasions, dose attenuations are multiplicative. That is, if toxicity 1 requires reduction to 75% dose and toxicity 2 requires reduction to 50% dose, presence of both toxicity 1 and toxicity 2 requires 37.5% dose. In the second place, there can be conflict in the algorithms for managing toxicities. A protocol may specify that, for toxicity 1, suspend drug until the patient recovers and then give 75% of previous dose, and that, for toxicity 2, reduce drug dose to 75% of the previous dose and escalate dose back to full dose if patient recovers.

7. The eligibility criteria of a clinical trial are *entry* criteria that, once a patient enrolled, can be ignored. This is conceptually distinct from the *applicability* criteria of guidelines that a patient must satisfy if the guideline is relevant for the patient.

8. A phase-1 clinical trial seeks to find the maximum tolerated dose of a drug regimen. Thus, the dose to be given to a patient may depend on reactions that other patients have to the drugs. Thus, you need to query data from other patients when you compute the dose for a particular patient.