Representing and Reasoning with Temporal Constraints in Clinical Trials using Semantic Technologies

Ravi D. Shankar[1], Susana B. Martins[1], Martin J. O'Connor[1], David B. Parrish[2] and
Amar K. Das[1]

[1]Stanford Medical Informatics, Stanford University
251 Campus Drive, MSOB X215, Stanford, California, USA
{ravi.shankar, smartins, moconnor, amar.das}@stanford.edu
[2]Immune Tolerance Network, Pittsburgh, Pennsylvania, USA
dparrish@immunetolerance.org

Abstract. Clinical trial protocols include schedule of clinical trial activities such as clinical tests, procedures, and medications. The schedule specifies temporal constraints on the sequence of these activities, on their start times and duration, and on their potential repetitions. There is an enormous requirement to conform to the constraints found in the protocols during the conduct of the clinical trials. In this paper, we present our approach to formally represent temporal constraints found in clinical trials, and to facilitate reasoning with the constraints. We have identified a representative set of temporal constraints found in clinical trials in the immune tolerance area, and have developed a temporal constraint ontology that allows us to formulate the temporal constraints to the extent required to support clinical trials management. We use the ontology to specify temporal annotation on clinical activities in an encoded clinical trial protocol. We have developed a temporal model to encapsulate time-stamped data, and to facilitate interval-based temporal operations on the data. Using semantic web technologies, we are building a knowledge-based framework that integrates the temporal constraint ontology with the temporal model to support queries on clinical trial data. Using our approach, we can formally specify temporal constraints, and reason with the temporal knowledge to support management of clinical trials.

1 Introduction

Clinical trials are formal studies on participants to systematically evaluate the safety and efficacy of new or unproven approaches in the prevention and treatment of medical conditions in humans. A clinical trial protocol is a document that includes study objectives, study design, participant eligibility criteria, enrollment schedule, and study plan. It specifies a temporal schedule of clinical trial activities such as clinical tests, procedures, and medications. The schedule includes temporal constraints on the sequence of these activities, on their duration, and on potential cycles. A temporal constraint is defined as an interval-based temporal annotation on a domain entity in relationship with other entities. Temporal constraints are fundamental to the descriptions of protocol entities, such as the following specifications: *Participants will be enrolled at least two days apart; Participant is ineligible if he/she had vaccination with a live virus within the last 6 weeks before enrollment; The first dose will be infused over a minimum of 12 hours; Visit 10 for the participant occurs 3 weeks ± 2 days from the day of transplant.* There is an enormous requirement on the execution of a clinical trial to conform to the temporal constraints found in the protocol. Studies need to be tracked for the purposes of general planning, gauging progression, monitoring patient safety, and managing personnel and clinical resources. The tracking effort is compounded by the fact that a trial often is carried out at multiple sites, geographically distributed, sometimes across the world. The validity of the findings of the clinical trial depends on the clinical trial personnel and the participants performing clinical trial activities as planned in the protocol. More importantly, the treatment and assessment schedules should be strictly followed to ensure the safety of participants.

We have developed an ontological framework that we call Epoch [1,2], to support the management of clinical trials at the Immune Tolerance Network, or ITN [3,4]. As part of this effort, we have developed a suite of ontologies that, along with semantic inferences and rules, provide a formal protocol definition for clinical trial applications. We use the OWL Web Ontology language [5], which is a W3C standard language for use in Semantic Web where machines can provide enhanced services by reasoning with facts and definitions expressed in OWL. Central to our ontological effort is the modeling of temporal constraints that we identified in clinical trial protocols. We have created the *temporal constraint ontology* to formally represent temporal constraints. The ontological representation can then be used to construct rules that can be used in turn, for reasoning with temporal constraints. Thus, at protocol specification phase, a domain expert can capture the essence of temporal constraints using higher-level ontological constructs. At a later time, a software developer can fully encode the constraints by creating rules in terms of temporal patterns and other protocol entities in the ontologies. We are using SWRL, the Semantic Web Rule Language [6] to write the rules. At execution time of the protocol, the rule elements use the protocol knowledge specified in the Epoch ontologies, and the clinical trial data collected in the clinical trial databases to reason with the temporal constraints. In this paper, we discuss our work in identifying temporal constraints found in ITN's clinical trial protocols. We then discuss our temporal constraint ontology using some patterns that we found in the temporal constraints. We then show how we use the temporal constraint ontology along with

other Epoch ontologies to create rules that can be executed at runtime to support clinical trial management.

2   Temporal Constraints in Clinical Trials

A clinical trial protocol defines a protocol schema that divides the temporal span of the study into phases such as the treatment phase and follow-up phase, and specifies the temporal sequence of the phases. It also includes a schedule of activities that enumerates a sequence of protocol visits that are planned at each phase, and, for each visit, specifies the time window when the visit should happen and a list of clinical activities (assessments, procedures and tests) that are planned at that visit. Activities such as medication need not be confined to visits and can be planned to occur in a time window within a protocol phase. An activity can have sub activities that can impose additional temporal constraints. For example, an assessment activity can include collection and processing of biological specimens with its own set of temporal constraints.

Here is a representative set of temporal constraints that we found in the ITN protocols that we are encoding:

1. *Visit 17 must occur at least 1 week but no later than 4 weeks after the end of 2003 ragweed season.*
2. *Administer Rapamune 1 week from Visit 0 daily for 84 days.*
3. *Visit 1 should occur 2 weeks ± 3 days after transplant.*
4. *Screening visit evaluations must occur between 30 days prior to Visit -1 and 45 days prior to Visit 0.*
5. *The vital signs of the participant should be obtained at routine time points starting at 10 minutes post infusion, then at 20-minute intervals until the participant is discharged.*
6. *Administer study medication at weekly intervals for 3 months.*
7. *Clinical assessments are required twice a week until Day 28 or discharge from hospital.*
8. *The first and second blood draws are 10 days apart, and the third draw is 11-14 days after the second.*
9. *On days that both IT and omalizumab are administered, omalizumab will be injected 60 minutes after the IT.*
10. *Monitor cyclosporine levels 3 times per week while in-patient, then weekly as out-patient.*

As evident in the constraints, clinical activities —we are using the terms *activity* and *event* interchangeably— are temporally dependent on each other. The temporal annotations in the constraints are specified in relative terms typically with reference to one or more clinical events. At the protocol execution time, the actual times of these events found in the clinical data will be used to reason with the constraints. There can also be fuzziness in the relative start and end times as well as in the duration of the activity. An activity can be repeated at a periodic interval for a specific number of

times or until a condition is satisfied. The periodic interval can be a single offset or a set of offsets. The temporal annotation of an activity or the temporal ordering of activities can be conditional on other events.

3 Temporal Representation

We have developed a temporal constraint ontology that can be used to formally specify the temporal constraints found in the clinical trial protocols. We briefly describe the core entities of the underlying temporal representation below:

Anchor defines an unbound time point that can be used to specify temporal relations among activities. It can be used as a reference point to define the start of another event before or after the anchor. In example 1 (of the constraints listed earlier), *end of 2003 ragweed season* is an anchor used to define the start of *Visit 17*. During the execution of the protocol, an anchor is bound to the absolute time of the anchor as recorded in the clinical trial data.

Duration is the difference between two time points. It is used typically to specify how long an activity lasts. In example 2, *84 days* is the duration.

Anchored Duration relates two activities with a temporal offset. In example 2, the activity *administer Rapamune* is offset from the anchor *Visit 0* by *1 week*.

Varying Duration is defined as duration with a high variance and a low variance. In example 3, *2 weeks ± 3 days* specifies a varying offset between *transplant* time and *Visit 1* start time.

Start and End Expression constrains the start and the end of an activity and is expressed as offsets before or after one or more reference events. In example 4, the start of the activity *Screening visit evaluations* is 30 days before the anchor *Visit -1* and the end is 45 days before another anchor *Visit 0*.

Cyclical Plan Expression formulates events that are repeated at periodic intervals. The repetition ends typically when a specific number of cycles is reached or until a specific condition is satisfied. There are two types of cyclical plans with subtle differences. The first type has a single anchor point with potentially multiple intervals. In example 5, the *vital signs* assessments are planned at 10, 30, 60, 90, 120, and 180 minutes after *infusion*. If the participant gets off schedule because the assessment is made at minute 35 instead of minute 30, then the participant gets back on schedule with the next assessment at minute 60. This type of cyclical plan is used generally with assessments and tests where evaluations need to be made at specific intervals after a clinical intervention. The second type of cyclical plan can potentially have multiple anchors with a single offset. In example 6, the plan is to administer medication at weekly intervals for 3 months. The initial anchor is the event of administering the first dose. According to the schedule, the second dose will be 1 week later, and the third 1 week later from the second dose. If the participant gets off schedule because the drug was administered 5 days after first dose and not 7 days, then the participant gets back on schedule with the next dose at 7 days from the last dose. This type of cyclical plan is used typically with drug administration where fixed intervals between dosages need to be maintained for safety and efficacy purposes.

Conditional Expression allows associating different temporal annotations with a single activity based on a condition. There are three patterns of conditional expressions – *if-then, if-then-else* and *until-then* patterns. Example 9 illustrates the *if-then* pattern – the temporal constraint between the administrations of two drugs is dependent on the condition that the two drugs are administered on the same day. Example 10 illustrates the *until-then* pattern – the monitoring activity is performed 3 times a week until the participant is in in-patient status, and when the status changes to out-patient then the activity is performed weekly.

4 Epoch Ontologies

In order to support clinical trial management activities, the Epoch knowledge-based approach provides three methods: 1. knowledge acquisition methods that allow users to encode protocols, 2. ontology-database mapping methods that integrate the protocol and biomedical knowledge with clinical trial data including clinical results and operational data stored in the ITN data repository, and 3. concept-driven querying methods that support integrated data management, and that can be used to create high-level abstractions of clinical data during analysis of clinical results. At the center of all these methods is the suite of Epoch ontologies that provide a common nomenclature and semantics of clinical trial protocol elements:

- The *clinical trial ontology* is the overarching ontology that encapsulates the knowledge structure of a clinical trial protocol. It simplifies the complexity inherent in the full structure of the protocol by focusing only on concepts required to support clinical trial management. Other concepts are either ignored or partially represented..
- The *constraint expression ontology* models the class of temporal constraints (see Section 3) and logical constraints found in clinical trial protocols.
- The *virtual trial data ontology* encapsulates the study data that is being collected, such as participant clinical record, specimen workflow logs, and site related data. A mapping component can then map clinical trial data (found in a relational database) to these virtual data records using a mapping ontology. The data model concept is similar to the Virtual Medical Record [7] specification promoted in the clinical guideline modeling efforts.
- The *organization ontology* provides a structure to specify study sites, clinical and core laboratories, and bio-repositories that participate in the implementation of a specific protocol.
- The *assay ontology* models characteristics of mechanistic studies relevant to immune disorders. An assay specification includes the clinical specimen that can be analyzed using that assay, and the workflow of the specimen processing at the core laboratories.
- The *labware ontology* models a laboratory catalog that mainly lists specimen containers used in the clinical trials.
- The *measurement ontology* has concepts of physical measurements such as volume and duration, and units of measurement such as milliliter and month

4.1 Temporal model in the virtual trial data ontology

The *virtual trial data ontology* uses a valid-time model to represent the temporal component of clinical trial data. In this model, all facts have temporal extent and are associated with instants or intervals denoting the times that they are held to be true. The core concept in the model is the *extended proposition* class that represents information that extends over time. There are two types of extended propositions in the model: 1. *extended primitive propositions* that represent data derived directly from secondary storage, and 2. *extended abstract propositions* that are abstracted from other propositions. These extended propositions can be used to consistently represent temporal information in ontologies. For example, a set of participant visits in a clinical trial data can be represented by defining a class called *VisitRecord* that inherits the *valid time* property from *extended proposition* class. The *valid time* property will then hold a visit's actual occurrence time. Similarly, an extended primitive proposition can be used to represent a drug regimen, with a value of type string to hold the drug name and a set of periods in the valid time property to hold drug delivery times. A more detailed discussion of the temporal model can be found elsewhere in the literature [8].

5   Implementation using Semantic Technologies

We have developed the Epoch ontologies in OWL where *classes* encapsulate the protocol concepts, and *properties* relate the classes to each other. Clinical trial data can be represented as instances of classes —referred to as *individuals*. OWL is a powerful constraint language for precisely defining how concepts in ontology should be interpreted. The Semantic Web Rule Language (SWRL) allows users to write Horn-like rules that can be expressed in terms of OWL concepts, and that can reason about OWL individuals. SWRL provides deductive reasoning capabilities that can infer new knowledge from an existing OWL knowledge base. We use SWRL to specify temporal constraints. Once all temporal information is represented consistently using the temporal model, SWRL rules can be written in terms of this model and the temporal constraint ontology. However, the core SWRL language has limited temporal reasoning capabilities. A few temporal predicates called *built-ins* are included in the set of standard predicates, but they have limited expressive power. SWRL provides an extension mechanism to add user-defined predicates. We used this mechanism to define a set of temporal predicates to operate on temporal values. These predicates support the standard Allen temporal operators [9]. Using these built-in operators in conjunction with the temporal model, we can express complex temporal rules.
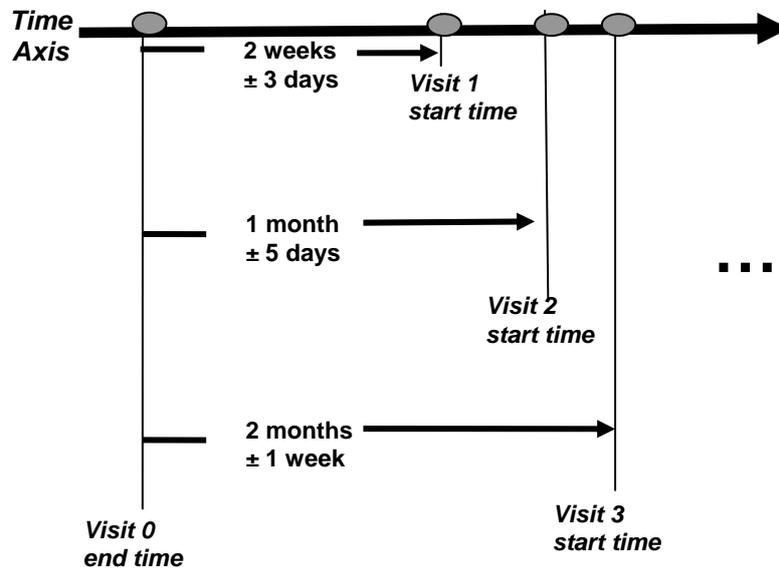
Figure 1 A sample visit schedule specifies temporal constraints on the visit start times

Here is an example SWRL rule to check if clinical trial participants conform to a visit schedule (Figure 1) specified in the protocol:

```
    Participant(?p) ^
    hasVisitRecord(?p, ?vr) ^
    hasVisitId(?vr, ?vid1) ^
    hasValidTime(?vr, ?vt) ^
    Visit(?v) ^
    hasVisitId(?vr, ?vid2) ^
    hasPlannedTiming(?v, ?pt) ^
    hasRelativeStartTime(?pt, ?st) ^
    swrlb:getStartInterval(?se, ?p, ?st) ^
    swrlb:equal(?vid1, ?vid2) ^
    temporal:inside(?vt, ?se) ^
-> ConformingParticipant(?p)
```

The rule uses concepts such as *Participant* and *Visit* from the *clinical trial ontology* and the concept of *Relative Start Time* as Anchored Duration in the *temporal constraint ontology*. The actual visits undertaken by a participant is encapsulated as the *VisitRecord* in the *virtual trial data ontology*, and is an extended proposition in the temporal model. The rule uses two built-ins – *equal*, that checks if two strings are

equal, and *inside*, which is a built-in that we developed to check if an absolute time is within a time interval (see Section 3). Protégé [10,11] is a software tool that supports the specification and maintenance of terminologies, ontologies and knowledge-bases in OWL. It has a plug-in called SWRL Tab [12], an editor for SWRL rules. We used Protégé to create the ontologies in OWL and SWRL. We then encoded specific protocols using Protégé's knowledge-acquisition facilities. The data generated from the implementation and execution of clinical trials is stored in a relational database. The types of data include participant enrollment data, specimen shipping and receiving logs, participant visits and activities, and clinical results. We have implemented a dynamic OWL-to-relational mapping method and have used SWRL to provide a high-level query language that uses this mapping methodology. A *schema ontology* describes the schema of an arbitrary relational database. A *mapping ontology* describes the mapping of data stored in tables in a relational database to entities in an OWL ontology. A *mapping software* uses the data source and the mapping ontologies to dynamically map trial data to entities in the *virtual trial data ontology* (Figure 2). A detailed description of the mapping techniques can be found elsewhere in the literature [13]. We are currently using JESS [14], a production rule-engine, to selectively execute the SWRL rules based on the context. For example, the rule that specifies the constraint on a visit time window will alone need to be executed when checking if a specific participant's visit satisfied the constraint. Thus, a temporal constraint is defined first using the temporal constraint ontology, then is formulated as a rule, finally, is reasoned with real clinical data using dynamic mappings between ontological concepts and relational database elements.
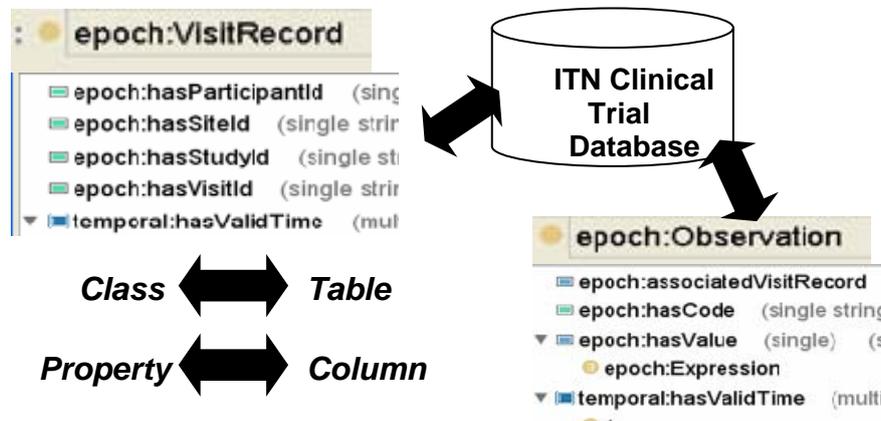

Figure 2 The OWL classes and properties of the *virtual trial data ontology* is mapped to tables and columns of a clinical trial database using the model-database mapper

6 Related Work

Over the years, many expressive models have been developed to represent temporal constraints [15-18]. Shahar's approach [19] identifies temporal abstractions of data and properties using interpolation-based techniques and knowledge-based reasoning. In recent years, there have been a number of initiatives to create clinical trial protocol models that encapsulate clinical trial activities and associated temporal constraints found in a protocol. These ontologies are then used to automate different clinical trial management activities such as eligibility determination, participant tracking, and site management. The ontologies can also be used when subsequently analyzing the clinical trial data. Our Epoch framework employs a task-based paradigm that combines an explicit representation of the clinical trial domain with rules that capture the logical conditions and temporal constraints found in the trial management process. There have been a number of proposals on task-based clinical guideline representation formats – EON [20], PRO*forma* [21], GLIF [22], etc. that deal with temporal constraints on patient data and on activities found in clinical guidelines.

In the area of clinical trials, several modeling efforts have addressed different requirements of trial management activities. An ontology to represent temporal information and cyclical event patterns in clinical trial protocols has been proposed by Weng et al. [23]. The Trial Bank Project [24] is a trial registry that uses a protocol ontology to capture information such as intervention, outcomes, and eligibility criteria on randomized clinical trials. The underlying knowledge base can support systematic reviewing and evidence-based practice.

There is an ongoing effort by CDISC [25], an industry-lead, multidisciplinary organization, to develop and support the electronic acquisition, exchange, submission and archiving of clinical trials data. As part of this effort, CDISC is developing the Structured Protocol Representation that identifies standard elements of a clinical trial protocol that can be codified to facilitate the data interchange among systems and stakeholders including regulatory authorities, biopharmaceutical industry, statisticians, project managers, etc. A parallel effort is the BRIDG [26,27] project, a partnership of several organizations including CDISC, the HL7 standards body [28], the National Cancer Institute and the Federal Drug Administration, that consumes the Trial Design Model work to build a comprehensive domain analysis model representing protocol-driven biomedical/clinical research. The BRIDG model is a work in progress to elaborately define functions and behaviors throughout clinical trials, and uses the Unified Modeling Language (UML) for representation. The model, in its current state, lacks formalization of and reasoning with temporal constraints, and thus, cannot fully support the requirements of ITN's clinical trial management.

7 Discussion

The increasing complexity of clinical trials has generated an enormous requirement for knowledge and information management at all stages of the trials – planning, specification, implementation, and analysis. Our focus is currently on two application areas: 1. tracking participants of the trial as they advance through the studies, and 2.

tracking clinical specimens as they are processed at the trial laboratories. The core of the Epoch framework is a suite of ontologies that encodes knowledge about the clinical trial domain that is relevant to trial management activities. Our focus on supporting trial management activities is also reflected in our approach to temporal constraint reasoning. Thus, in developing the temporal constraint ontology and in our reasoning approach with rules, we limited ourselves to the types and of temporal constraints, to the complexity of formalism and to the levels of reasoning required to support clinical trial management activities. For example, we do not support checking temporal constraints for consistency in the encoded clinical trial knowledge. We continue to work on the *temporal constraints ontology* to support newer and more complex constraints. With any complex constraint, one concern is the power, or lack thereof, of our reasoning approach with SWRL rules.

Since we use OWL ontologies and SWRL rules, native RDF Store (storing data as RDF triples) would have been a natural solution for storing clinical trial data, and then seamlessly operate on the data using our ontologies and rules. ITN uses a legacy relational database system to store clinical trial data, and therefore, prevents us from using native RDF Stores as our backend. We have built techniques to map the database tables to our *virtual trial data ontology* OWL classes. With these solutions, our data model remains flexible and independent of the structure of the data sources. We are yet to undertake a thorough evaluation of our dynamic mapping methodology especially in the area of scalability.

An often over-looked aspect of knowledge-based reasoning approaches is the task of knowledge-acquisition. Currently, we use the Protégé-OWL editor to build the Epoch models. Based on the class and property definitions, Protégé automatically generates graphical user interface (GUI) forms that can be used to create instances of these classes (OWL *individuals*). Thus, domain specialists can use to enter a specification of a protocol, say for a transplant clinical trial, using these Protégé generated forms. Unfortunately, domain specialists find it cumbersome and non-intuitive to use the generic user interfaces as they are exposed to the complexities of the Epoch ontologies, the OWL expressions and the SWRL rules. We are building custom graphical user interfaces that hide the complexities of the knowledge models, and that facilitate guided knowledge-acquisition. Providing a friendly user interface to enter SWRL rules can be challenging though.

The knowledge requirements borne out of the need for managing clinical trials align well with the touted strengths of semantic web technologies – uniform domain-specific semantics, flexible information models, and inference technology. Using these technologies, we have built a knowledge-based framework for temporal constraints reasoning that is, above all, practical.

References

1. Shankar, R.D., Martins, S.B., O'Connor, M.J., Parrish, D.B., Das, A.K.: Epoch: an ontological framework to support clinical trials management. Proceedings of the International Workshop on Health Information and Knowledge Management, 25–32 (2006)
2. Shankar, R.D., Martins, S.B., O'Connor, M.J., Parrish, D.B., Das, A.K.: Towards Semantic Interoperability in a Clinical Trials Management System. Proceedings of the Fifth International Semantic Web Conference. 901-912 (2006)
3. Immune Tolerance network, http:///www.immunetolerance.org
4. Rotrosen, D., Matthews, J.B., Bluestone, J.A.: The Immune Tolerance Network: a New Paradigm for Developing Tolerance-Inducing Therapies. Journal of Allergy and Clinical Immunology, 110(1):17-23 (2002)
5. OWL, http://www.w3.org/2004/OWL
6. SWRL, http://www.w3.org/Submission/SWRL
7. Johnson, P.D., Tu, S. W., Musen, M. A., Purves, I.: A Virtual Medical Record for Guideline-Based Decision Support. Proceedings of the 2001 AMIA Annual Symposium, 294-298 (2001)
8. Snodgrass, R.T. (Ed).: The TSQL2 temporal query language. Kluwer Academic Publishers, Boston (1995)
9. Allen, J.F. Maintaining knowledge about temporal intervals. Communications of the ACM, 26(11): 832-843 (1993)
10. Protégé, http://protege.stanford.edu
11. Knublauch, H. Fergerson, R.W., Noy, N.F., Musen, M.A.: The Protégé OWL Plugin: An Open Development Environment for Semantic Web applications. Proceedings of the Third International Semantic Web Conference. 229-243 (2004)
12. O'Connor, M.J., Knublauch, H., Tu, S.W., Grossof, B., Dean, M., Grosso, W.E., Musen, M.A.: Supporting Rule System Interoperability on the Semantic Web with SWRL. Proceedings of the Fourth International Semantic Web Conference. 974-986 (2005)
13. O'Connor, M.J., Shankar, R.D. Tu, S.W., Nyulas, C., Musen, M.A., Das, A.K.: Using Semantic Web Techonologies for Knowledge-Driven Queries in Clinical Trials. Proceedings of the 11th Conference on Artificial Intelligence in Medicine (2007)
14. JESS, http://www.jessrules.com
15. Bettini, C., Jajodia, S., Wang, X.: Solving multi-granularity constraint networks. Artificial Intelligence, 140(1-2):107-152 (2002)
16. Combi, C., Franceschet, M., and Peron, A,: Representing and Reasoning about Temporal Granularities. Journal of Logic and Computation, 14(1):51-77 (2004)
17. Terenziani, P.: Toward a Unifying Ontology Dealing with Both User-Defined Periodicity and Temporal Constraints About Repeated Events, Computational Intelligence 18(3):336-385 (2002)
18. Duftschmid, G., Miksch, S., Gall, W.: Verification of temporal scheduling constraints in clinical practice guidelines. Artificial Intelligence in Medicine 25(2): 93-121 (2002)
19. Shahar Y., Musen, M.A.: Knowledge-Based Temporal Abstraction in Clinical Domains. Artificial Intelligence in Medicine,8:267-298 (1996)

20. Musen, M.A., Tu, S.W., Das, A.K., Shahar, Y. EON: A component-based approach to automation of protocol-directed therapy, Journal of the American Medical Informatics Association, 3(6): 367–388 (1996)
21. Fox, J., Johns, N., Rahmanzadeh, A., Thomson, R.: PRO*forma*: A method and language for specifying clinical guidelines and protocols. Proceedings of Medical Informatics Europe (1996)
22. Boxwala, A.A., Peleg, M., Tu, S. W., Ogunyemi, O., Zeng, Q. T., Wang, D., Patel, V. L., Greenes, R. A., Shortliffe, E. H.: GLIF3: A Representation Format for Sharable Computer-Interpretable Clinical Practice. Journal of Biomedical Informatics, 37(3):147-161 (2004)
23. Weng, C., Kahn, M., Gennari, J.H.: Temporal Knowledge Representation for Scheduling Tasks in Clinical Trial Protocols. Proceedings of the American Medical Informatics Association Fall Symposium. 879 – 883 (2002)
24. Sim, I., Olasov, B., Carini, S.: The Trial Bank system: capturing randomized trials for evidence-based medicine. Proceedings of the American Medical Informatics Association Fall Symposium. 1076 (2003)
25. CDISC, http://www.cdisc.org
26. BRIDG, http://www.bridgproject.org
27. Fridsma, D.B., Evans, J., Hastak, S., Mead, C.N.: The BRIDG project: a technical report. Journal of American Medical Informatics Association. 15(2):130-137 (2007)
28. HL7, http://www.hl7.org