Ontology-based temporal analysis for medical device adverse event— a use case study on Late Stent Thrombosis

Kim Clark[1], Deepak Sharma[2], Rui Qin[2], Guoqian Jiang[2], Christopher G. Chute[2], Cui Tao[2,3*]

[1]Boston Scientific Corporation, Maple Grove, MN
[2]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN
[3]School of Biomedical Informatics, University of Texas Health Science Center at Houston Houston, TX
* Corresponding author email: cui.tao@uth.tmc.edu

Abstract. In this paper, we show how we have applied the Clinical Narrative Temporal Relation Ontology (CNTRO) and its associated temporal reasoning system (the CNTRO Timeline Library) for automatically identifying, ordering, and calculating the duration of temporal events within adverse event report narratives. The Objective of this research is to evaluate the feasibility of the CNTRO Timeline Library using a real clinical use case application (late stent thrombosis adverse events). Narratives from late stent thrombosis adverse events documented within the Food and Drug Administration's (FDA) Manufacturing and User Facility Device Experience (MAUDE) database were used as a test case. 238 annotated narratives were evaluated using the CNTRO Timeline Library. The CNTRO Timeline Library had a 95.38% accuracy in correctly ordering events within the narratives. The duration function of the CNTRO Timeline Library was also evaluated and found to have 80% accuracy in correctly determining the duration of an event across 41 narratives, and 76.6% accuracy in determining the duration between two given events across 77 narratives. Within this paper is an example of how the durations calculated by the CNTRO Timeline Library can be used to examine therapeutic guidelines. Complaint narratives were separated into two groups based on a long (greater than 6 months) or short (6 months or less) duration of antiplatelet therapy administration. The duration of antiplatelet administration was then compared to the duration between stent implantation and occurrence of late stent thrombosis. The goal of this analysis was to show how the CNTRO ontology and is associated Timeline Library could be used to examine recommendations for length of drug administration. In this use case, the result supports guidance for use of longer antiplatelet therapy. This example validates the CNTRO System's ability to confirm known temporal trends.

1 Introduction

The Food and Drug Administration (FDA) requires notification of all medical device adverse events that are associated with malfunction, serious injury, or death [1]. Events leading up to the device failure are compiled and reported in a narrative text, and made publically available through the MAUDE (Manufacturer and User Facility Device Experience) database [4,5]. Temporal patterns may exist (potentially including similar sequences of events, similar durations of or between events, or similar time/date stamps of event occurrences), but are often buried with the text of the narratives. Analysts at the Center for Devices and Radiological Health (CDRH) read the event histories of each report looking for trends within narratives of similar adverse event failure modes [6]. With 80,000 to 120,000 device-related adverse

events reported annually to the FDA [7], this method for monitoring adverse events is time consuming, expensive, and the potential exists for a missed pattern observation. An automated temporal analysis of adverse event narratives would lead to faster identification of patterns, earlier prediction of a future failure, and could be used to drive improvements into the next generation of medical devices.

Within this paper, we propose the use of the Clinical Narrative Temporal Relation Ontology (CNTRO) [2], with its associated temporal reasoning framework (The CNTRO Timeline Library) [3,8] to facilitate an efficient and semi-automated temporal analysis of medical device adverse events obtained from the FDA's MAUDE database [4,5]. Previously, we have shown how CNTRO can be combined with LifeFlow [9], software developed by the University of Maryland that is capable of visualizing event sequences, to see patterns in the order of events within several narratives [10]. We have also shown CNTRO's ability to correctly answer temporal-related questions regarding events that have occurred within a narrative [11]. The goal of this present article is to illustrate how the CNTRO system (refers to the ontology and its associated Timeline Library) can be used to analyze temporal properties of events that are documented across multiple narratives of adverse events.

Many previous efforts have been made for time information and temporal relation modeling in computer-based systems. Furia et al. surveyed these approaches and carefully compared their adoptions in different applications [12]. The authors of this survey then concluded that the usage of formal time models should be domain specific since the time expression, abstraction, and reasoning can be varied across different applications. This claim has been agreed by other researchers, especially for the complex and unique clinical data [13,14]. A few modeling approaches have been applied to represent the temporal information in clinical data. Many of them focus on a specific task such as temporal reasoning on discharge summaries [15], temporal extraction on eligibility criteria [16], or for time delayed mutual information over populations [17]. Ontologies such as Time ontology [18] and the SWRL Temporal ontology [19] can formally model temporal information in general and connect with semantic reasoners for inferring new temporal relations based on the semantics defined in the ontologies. These ontologies, however, only focus on structured data with absolute time information and therefore cannot precisely capture the temporal information expressed in human language [20]. In clinical narratives, many temporal features are expressed in relative (e.g., next Friday) or ambiguous (e.g. early last week) ways. Ignoring this data will forgo a lot of valuable information that could be otherwise leveraged in clinical research. Models such as the HL7 time specification [21] and the TimeML model [22] offer a way to represent temporal information originally from semi-structured or unstructured narratives. These approaches, however, do not provide formal semantic definition capacities for domain knowledge as ontologies do. In clinical narratives, much temporal information is not explicitly expressed, but rather needs to be inferred before the data can be further analyzed. Without a reasoning component, it is difficult to resolve a relatively complete patient history for profound clinical studies [23]. Therefore, we believe that the CNTRO system is necessary since it provides a formal ontology in OWL with well-defined semantics for the time domain and enables semantic-web [24] based temporal reasoning.

In this article, we use the Late Stent Thrombosis (LST) use case to demonstrate how to apply the CNTRO system on temporal relation reasoning and temporal analysis. Although the exact mechanism or mechanisms of LST are not known, it has been observed to occur less frequently when dual antiplatelet therapy has been administered over a period of time [25,26]. Current guidelines recommend the administration of dual antiplatelet therapy for 3 to 6 months following drug-eluting stent implantation, unless the patient is not at high risk for bleeding, in which case therapy is recommended for 12 months [2]. We used the CNTRO System to evaluate events over the timeline and query both the duration in which antiplatelet therapy was administered for in each adverse event narrative and the duration between the initial stent implantation and the occurrence of late stent thrombosis. This work provides an example of how the CNTRO system is able to understand temporal information from multiple narrative files can be used to identify and confirm temporal trends.

A computer program cannot create a timeline of events and answer time-related questions by querying information directly from a narrative without semantic annotation and inference. Human experts can understand temporal relationships through the use of words such as "before", "after", "during", "following", etc, and appreciates that 1 year, 12 months, and 365 days are approximately equivalent even though differences in granularity are used. To allow for a "machine-understandable" data representation and exchange of temporal information automatically, the CNTRO System uses a Semantic-Web [24] based framework to apply relationships between events within natural language narratives through the use of the RDF (Resource Description Framework) triple representation [2]. An RDF triple consists of a subject, an object, and a predicate, which indicates the relationship between the subject and the object[6].

Consider the following example. "*60 days after stent implantation, antiplatelet therapy was discontinued in preparation for a splenectomy surgery*." In this example, stent implantation is identified as the subject, antiplatelet therapy discontinuation is identified as the object, and "after" is identified as the predicate. CNTRO is able to recognize the granularity of 60 days as equivalent to two months. A temporal relationship is created between stent implantation and discontinuation of antiplatelet therapy using a temporal offset of two months.

The computer program now "understands" that stent implantation occurred first, and discontinuation of antiplatelet therapy occurred second. It also "understands" that the time delay between these two events was two months. Additionally, there is an inference that because atniplatelet therapy was stopped, it had to have started at some point. Unless explicitly stated, it is inferred that therapy began on the day of stent implantation. The CNTRO framework then creates a timeline for events and provides a programmatic query interface to access the timeline information. This makes it easy for the time-related information to be queried in an automated manner. In our particular example, we could ask questions such as: Which event occurred first? How long after stent implantation was antiplatelet therapy administration discontinued?

2 Methods

2.1 The CNTRO System

CNTRO [2] is an OWL ontology designed to model temporal relations among clinical events. Figure 1 shows the ontology overview. It models clinical events, temporal entities (such as time instants, time intervals, repeated time periods, and durations), time granularity (such as minute, hour, day, month, year), temporal relationships, and time uncertainties in the semantic web notation. In order to facilitate users to annotate events and time-related information using CNTRO semantics, we have also implemented a Protégé plug-in, called Semantator [27]. The annotated information can be stored as an OWL/RDF file or in an RDF triple store. The annotated data can then be run through the CNTRO Timeline Library to infer temporal information that is not explicitly expressed in the original documents [3]. The CNTRO Timeline Library contains a rule-based normalizer which automatically converts different temporal expressions into standard formats. It also leverages the semantic definitions in the ontology (e.g., OWL DL axioms, property transitivity and inversions) to support temporal relation inference. In addition, the Timeline Library contains a set of Java functions for answering a list of time-related questions such as when a particular event happened, chronological sequence of events, durations of events, durations between events, and temporal relations between events.

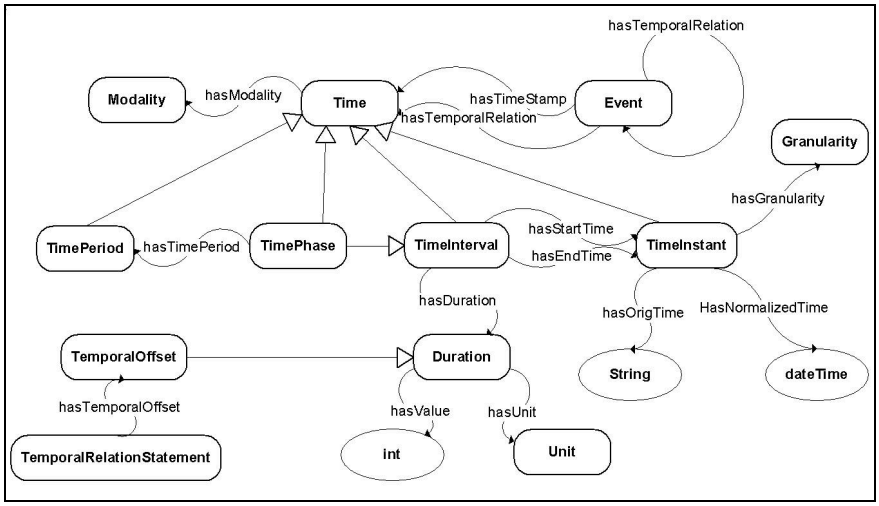

Figure 1: CNTRO Overview

2.2 Late Stent Thrombosis Adverse Event Identification

Medical device adverse event narratives resulting in late stent thrombosis were obtained from the MAUDE database for the years 2004 through 2010. 2004 was selected because this was the first full year following the initial drug-eluting stent (Cypher) launch within the United States [4]. Adverse events were filtered by device manufacturer and brand name as there are a limited number of drug-eluting stent devices commercially available within the United States.

The FDA provides some sortable failure modes within the MAUDE database; however, late stent thrombosis is not included as a failure mode. This is a weakness within the MAUDE database, but not the focus of the paper. To find the adverse

events that resulted in late stent thrombosis, a text search for “thrombosis” and “LST” was executed. Approximately 65% of the returned narratives were further filtered out due to thrombosis not being confirmed, thrombosis occurred less than 30 days following stent implantation (indicating thrombosis was acute and not late), and / or the narrative did not specify the duration or define the duration as “late”. The resulting narratives documenting occurrence of late stent thrombosis were then annotated.

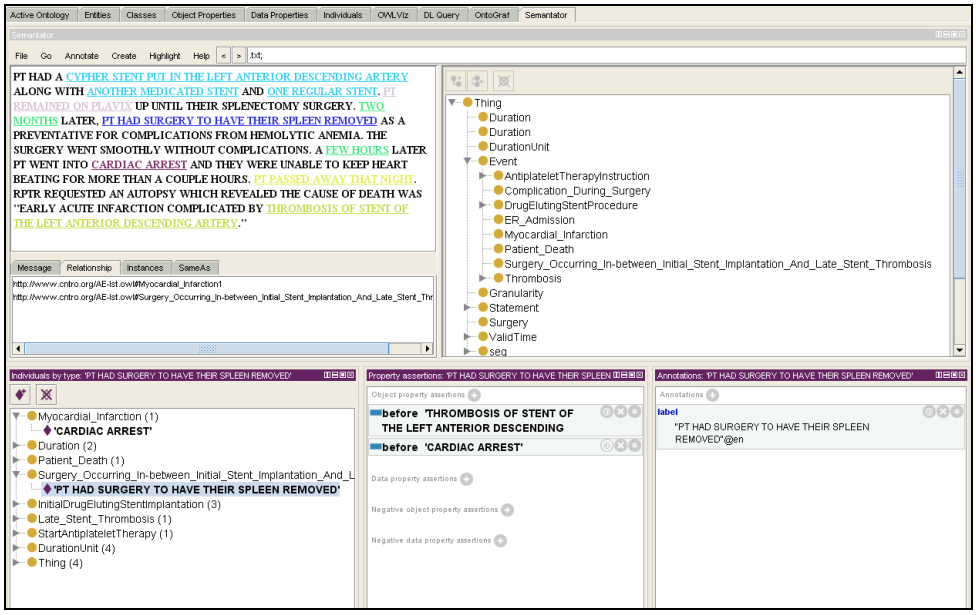

Figure 2: Semantic Annotation Using Semantator

2.3 Adverse Event Narrative Annotation

We created a domain ontology including common events occurring after stent implantation with specific normalized event types. The specialized cases of temporal events were imported into CNTRO for temporal relationship modeling. The following events were included: initial stent implantation, follow up stent implantation(s), start and stop time points of antiplatelet therapy administration, unrelated surgeries occurring after stent implantation, late stent thrombosis, myocardial infarction, admission to the emergency room, and patient death. The duration between initial stent implantation and occurrence of thrombosis is used as the output of the survival analysis performed within this paper. The start and stop points of antiplatelet therapy are required to determine the duration of therapy, which is used as a factor in the survival analysis. Follow-up stent implantations, unrelated surgeries (a common reason to stop antiplatelet therapy early), myocardial infarction, admission to the emergency room, and patient death were included within the annotations to verify the Event Order and Inferred Relationship functions of the CNTRO Timeline Library. Events such as guide wire insertion, which may have been documented in the adverse event report, are required for all stenting procedures;

therefore annotation of these events would not be beneficial and this was not performed. Life-saving events following the detection of thrombosis were not annotated either, as this use case investigates understanding why late stent thrombosis occurs and not the potential to survive the adverse event.

The LST adverse event files we identified were annotated using Semantator to identify the above events and their temporal features. Each adverse event file resulted in an OWL file which embedded the annotated results. Figure 2 shows a screenshot of the Semantator annotation environment. The top left panel shows the narrative being annotated, the top right panel shows the domain ontology with CNTRO imported, and the bottom three panels show some of the annotation results. As we can see, each event of interest or temporal expression can be annotated as OWL individuals with respect to one or more ontology classes. Individuals of different classes are displayed in different colors. Relations between these individuals can also be created using Semantator.

2.4 CNTRO Timeline Evaluation

For each annotated LST narrative, the CNTRO timeline library creates a matrix that visually shows the temporal relationships between the events, which is a simple way to track, view, document, and evaluate the accuracy of CNTRO system timeline computations. Each annotated event is included within the matrix. The matrix indicates which events occur at the same time, and then orders the remaining events on a timeline as applicable.

The annotations of the Late Stent Thrombosis Adverse Event Narratives were reviewed using these matrices and compared against the manually-annotated gold standard results. The gold standard annotations were evaluated by at least two human experts. The conflicts of the annotation were resolved after discussions among the human experts.

2.5 CNTRO Duration Evaluation

Durations can be computed for an individual event, between two events, or between an event and a timestamp. CNTRO first determines if 'start' and 'end' time information exists for an event to calculate the duration. If one of these pieces of information is missing, the program then computes it by either using a duration annotation, "*Antiplatelet therapy was administered for two months*" (the antiplatelet therapy event is defined here with a duration of 2 months) or uses a temporal relation to another event with a relative time stamp, "*Antiplatelet therapy was started in May 2006. In July 2006, the patient underwent prostrate surgery. Antiplatelet therapy was stopped the day before surgery."* In this second example the occurrence of antiplatelet therapy starting and stopping each have a time stamp, and CNTRO infers that antiplatelet therapy was administered for 2 months based on the duration between the start and end times. In some cases, the duration of a pair of events cannot be calculated directly (the two events are not directly connected through the RDF graph), but need to go through one or more intermediate events. In this case, the above two functions need to be called iteratively until the duration of the two events are calculated.

The adverse event narratives for late stent thrombosis could describe durations in days, months, and/or years. Month was the most frequent granularity used in the complaint data, followed by years, and then days. To be able to compare data from different narratives, the duration granularity was normalized to 'Month' for this use case as this was the most frequently used granularity, and estimating durations reported in years by number of days would likely increase the noise within the data. To normalize durations reported in days, the duration was divided by 30 and rounded. To normalize durations reported in years, the durations were multiplied by 12. Durations can also be calculated from start and end time stamps of a particular event or time stamps of two events. In some narratives, timestamps were reported with a granularity of 'Year.' (In example – "Stent implantation occurred in 2006 and thrombosis occurred in 2008.") The potential range of duration between these events could be anywhere between 12 months (if the stent implantation occurred in December 2006 and the thrombosis occurred in January 2008) and 24 months (if the stent implantation occurred in January 2006 and the thrombosis occurred in December 2008). The average potential duration was used in this type of narration, (in the above example, 18 months). The durations calculated by CNTRO were compared to manual calculations to determine accuracy.

2.6 Application of CNTRO Temporal Analysis

To provide an example of how the CNTRO system can potentially be used to evaluate temporal properties within narrative data, survival analysis was performed using the narratives that specified both a duration of antiplatelet therapy and time from stent implantation to late stent thrombosis (or in which a duration could be inferred) to examine therapeutic guidelines for antiplatelet administration duration. Note that as this data come from the FDA MAUDE Database, all records within the example ended up with an event of late stent thrombosis. Data of patients who have not had a late stent thrombosis occurrence are not easily accessible; therefore this example is purely illustrative of the CNTRO system's capability. Similarly, because the data used within this analysis comes from adverse event files indicating thrombosis occurred, no patient data requires censoring.

Late Stent Thrombosis adverse event files were divided into two different groups based on how long antiplatelet therapy was administered in patients following implantation of a drug-eluting stent. Using current antiplatelet therapy recommendations, any adverse event narrative specifying that antiplatelet medication was administered for less than 6 months was segregated into the Shorter Duration of Antiplatelet Therapy group. Any adverse event narrative indicating that antiplatelet medication was administered for 6 or more months was segregated into the Longer Duration of Antiplatelet Therapy group. Adverse event narratives that did not provide information specifying how long antiplatelet therapy was prescribed were excluded from the analysis.

3 Result

3.1 CNTRO Timeline and Duration Evaluation

There were 238 late stent thrombosis adverse event narratives contained enough event information such that a timeline could be created within CNTRO for system evaluation. For each report, we compared the CNTRO system inferred timeline with the gold standard result. The system was able to provide the correct results for all but 8 files. This resulted in an overall CNTRO timeline accuracy of 95.38%.
There were 41 late stent thrombosis adverse event narratives that included information such that the duration of antiplatelet therapy was known. The CNTRO automatic reasoning system had an 80% accuracy in inferring / calculating this duration of an event. There were 77 late stent thrombosis adverse event narratives included information such that the duration between stent implantation and late stent thrombosis was known. The CNTRO automatic reasoning system had a 76.3 % accuracy in inferring / calculating this duration between events. An analysis of the errors and discussion of possible enhancements to the CNTRO system is included within the Discussion section.

3.2 Late Stent Thrombosis Adverse Event Temporal Pattern Analysis

Within this paper, the CNTRO system was used to confirm what has been previously identified as temporal patterns within the late stent thrombosis adverse event in a semi-automated manner, which is more efficient than through manual observation. The common event pattern within late stent thrombosis adverse events (stent implantation, administration of antiplatelet therapy, discontinuation of antiplatelet therapy, late stent thrombosis) was shown by CNTRO system through timeline identification of events. This result shows that the CNTRO system has the potential to be applied across multiple adverse event failure modes to identify new trends that have previously not been observed.

3.3 Late Stent Thrombosis Survival Analysis

There were 36 late stent thrombosis adverse events that included both the duration between drug-eluting stent implantation and occurrence of late stent thrombosis, and a duration of antiplatelet therapy. These 36 reports were used to execute a survival analysis. Although this represents only a limited subset of late stent thrombosis events, the data can still be used for illustration purposes of CNTRO's temporal analysis capabilities. Late Stent Thrombosis adverse event files were divided into two different groups based on how long antiplatelet therapy was administered in patients with an implanted drug-eluting stent. Per the current guidelines, following drug-eluting stent implantation, patients should take antiplatelet therapy for 3 to 6 months, unless the patient is not at high risk for bleeding, in which case therapy is recommended for 12 months [28]. In our case, we considered 2 different groups: shorter Antiplatelet Therapy duration group (antiplatelet medication was administered for less than 6 months) and longer Antiplatelet Therapy duration group (antiplatelet medication was administered for 6 or more months). Adverse event narratives that did not provide information specifying how long antiplatelet therapy was prescribed were excluded from the analysis. 14 adverse events reported that antiplatelet therapy was administered for 6 months or less following initial stent implantation. 22 adverse events reported that antiplatelet therapy was administered greater than 6 months.

Survival analysis with Kaplan-Meier curve and log-rank test was performed in Minitab. The median time to LST is 27.3 months for longer antiplatelet therapy group and 14.6 months for shorter antiplatelet therapy group, respectively. The p-value of log-rank test is 0.029, which indicates a significant association between duration of antiplatelet therapy and time to LST. Figure 3 displays that late stent thrombosis occurs later in patients who continued to take antiplatelet therapy longer than 6 months. Although this is a retrospective observational study of a subset of LST cases only, the finding is consistent and supports guidance for use of longer antiplatelet therapy [2]. This example validates the CNTRO System's ability to confirm known temporal trends.

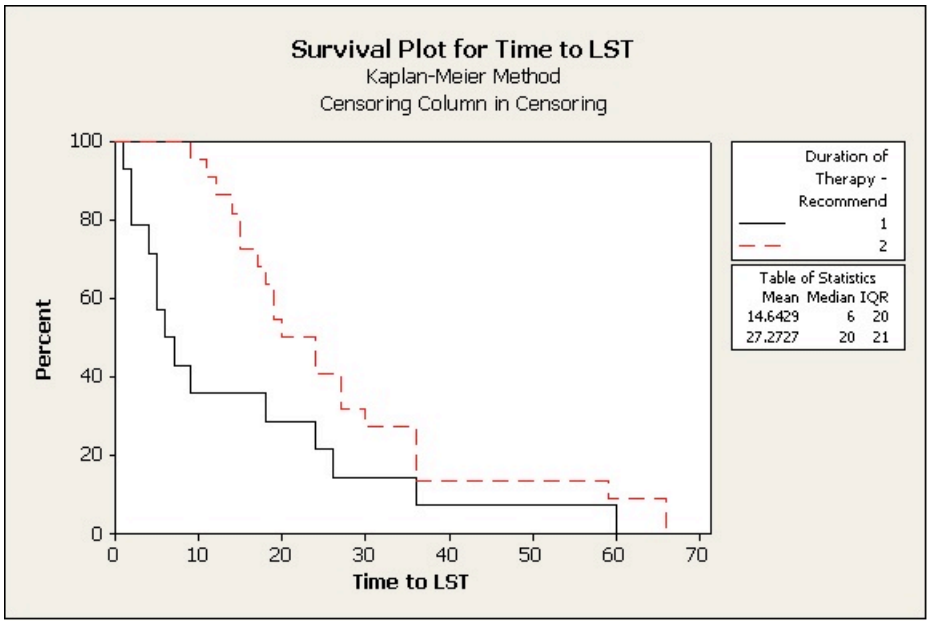

Figure 3: Survival analysis of shorter duration of antiplatelet therapy (group 1) and longer duration of antiplatelet therapy (group 2) in late stent thrombosis adverse events

4 Discussion

The CNTRO system was able to order the event sequences for 95.3% of the narratives. A few cases failed due to different interpretations of time intervals. Computing the order of two events is difficult when using 'start' or 'finish' temporal relations when both the start and end times are missing from the annotation. For example, a narrative might specify that antiplatelet therapy began at the time of stent implantation, and specify that it occurred for a period of 2 months. The temporal relation of the event1 (antiplatelet therapy) and event2 (stent implantation) depends on whether we compare by them the start time or the end time of the events. By

considering start time, the two events start at the same time (event1 starts event2). The system cannot infer the relationship by the end time since the duration of "stent implantation" was not specified. Given the assumption that the stent implantation procedure cannot last for 2 months, we can infer that event1 ends after event2. This kind of background knowledge needs to be further specified in the domain ontology so that the CNTRO system can infer the correct order. For example, "patient death" has to be the last event, which occurs in the patient-care timeline. This kind of inherited order needs to be incorporated in the domain ontology so that the sequence of events can be inferred.

For duration inference, there are three major reasons the program failed to return the correct results. (1) Annotation ambiguities: some narratives contain duration information in an ambiguous way such as in range (e.g., 2-3 month), or in different levels of granularity (e.g., "two month and 3 days") that the program cannot automatically process; (2) Long series of events: sometimes the duration calculation involves a long series of events. The program fails when there is more than one intermediate event between the start and the end events and the series of events involve combination of different temporal relations and/or absence of any temporal information of from an intermediate event; (3) Temporal relation granularity: an annotator can specify the level of granularity over a temporal relation. For example, we can specify that the granularity of "event1 before event2" is "day". This means that the temporal relation was compared on the granularity of day, which implies that although event1 was before event2, but they happened on the same day. This assumption was not programmed in the CNTRO system yet. This caused a few errors when calculating the duration. For example, we further know that event3 happened 183 days after event2. Without the assumption that event1 and event2 happened on the same day, the system cannot infer the duration between event1 and event3.

5 Conclusion

Although the CNTRO system can provide relatively good results for our use case, there are still limitations in the system. First, the evaluation results work well with the MAUDE reports because these reports are relatively short and simple compared to other clinical narratives such as clinical notes. More system evaluation of to be done for complex EHR data. Second, since the purpose of this study is to evaluate CNTRO's representation and reasoning capacities, the reports were annotated manually. The current manual annotation method is not practical for long-term use, and an automatic annotation process is currently under implementation. Third, many ambiguities and uncertainties were resolved during the annotation process. We are working on incorporating uncertainty reasoning in the CNTRO system. Nevertheless, this study provides promising results and valuable analysis for us to continue develop the CNTRO system.

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