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DATA DESCRIPTOR

The Leaf Clinical Trials Corpus: a new resource for query generation from clinical trial eligibility criteria

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Identifying cohorts of patients based on eligibility criteria such as medical conditions, procedures, and medication use is critical to recruitment for clinical trials. Such criteria are often most naturally described in free-text, using language familiar to clinicians and researchers. In order to identify potential participants at scale, these criteria must first be translated into queries on clinical databases, which can be labor-intensive and error-prone. Natural language processing (NLP) methods offer a potential means of such conversion into database queries automatically. However they must first be trained and evaluated using corpora which capture clinical trials criteria in sufficient detail. In this paper, we introduce the Leaf Clinical Trials (LCT) corpus, a human-annotated corpus of over 1,000 clinical trial eligibility criteria descriptions using highly granular structured labels capturing a range of biomedical phenomena. We provide details of our schema, annotation process, corpus quality, and statistics. Additionally, we present baseline information extraction results on this corpus as benchmarks for future work.

Background & Summary

Randomized controlled trials serve a critical role in the generation of medical evidence and furthering of biomedical research. In order to identify patients for clinical trials, investigators publish eligibility criteria, such as past history of certain conditions, treatments, or laboratory tests. These eligibility criteria are typically composed in free-text, consisting of inclusion and exclusion criteria. Patients meeting a trial's eligibility criteria are considered potential candidates for recruitment.

Recruitment of participants remains a major barrier to successful trial completion¹, so generating a large pool of potential candidates is often necessary. Manual chart review of hundreds or thousands of patients to determine a candidate pool, however, can be prohibitively labor- and time-intensive. Cohort discovery tools such as Leaf² and i2b2³ may be used, providing researchers with a relatively simple drag-and-drop graphical interface in their web browser to create database queries to find potential patients in electronic health records (EHR). Learning how to use such tools nevertheless presents a challenge, as graphically-represented concepts may not align with researchers' understanding of biomedical phenomena or trial eligibility criteria. In addition, certain complex queries may simply be impossible to execute due to structural limitations on the types of possible queries presented in these tools, such as complex temporal or nested sequences of events.

An alternative approach which holds promise is the use of natural language processing (NLP) to automatically analyze eligibility criteria and generate database queries to find patients in EHRs. NLP-based approaches have the advantage of obviating potential learning curves of tools such as Leaf, while leveraging existing eligibility criteria composed in a format researchers are already familiar with. Recent efforts to explore NLP-based approaches to eligibility criteria query generation have been published. These approaches can be generally categorized as (1) modular, multi-step methods which transform eligibility criteria into intermediate representations and finally into queries using rules⁴⁻⁶, (2) direct text-to-query generation methods using neural network-based semantic parsing^{5,6}, and (3) information retrieval approaches to detect relevant sections of free-text notes meeting a given criteria⁷⁻¹⁰.

For each category of NLP approaches, a key element for accelerating research efforts is large, robust corpora which capture eligibility criteria semantics sufficiently for high-accuracy query generation. Such corpora can

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Measure	EliIE ¹²	Chia ¹⁵	LCT Corpus
Disease domain	Alzheimer's Disease	All	All
No. of Eligibility Descriptions	230	1,000	1,006
No. of Annotations	15,596	68,174	105,816
No. of Entity types	8	15	50
No. of Relation types	3	12	51
Mean Entities per doc.	—	46	105
Mean Relations per doc.	—	19	49

Table 1. Annotation statistics for EliIE, Chia, and LCT corpora.

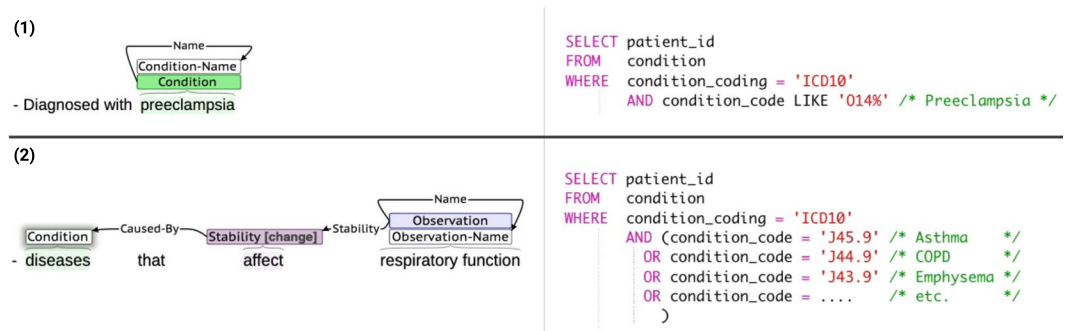


Fig. 1 Example eligibility criteria annotated using the LCT corpus annotation schema (left) and corresponding example SQL queries (right) using a hypothetical database table and columns. Annotations were done using the Brat annotation tool¹⁹. The ICD-10 codes shown are examples and not intended to be exhaustive.

serve as reliable benchmarks for purposes of comparing NLP methods as well as training datasets. A number of corpora designed for multi-step methods, which we focus on here, have been published. Past corpora cover only a modest number of eligibility criteria¹¹, are narrowly focused on certain diseases only¹², are not publicly available^{13,14}, or have annotations insufficiently granular to fully capture the diverse, nuanced semantics of eligibility criteria¹⁵. Yu *et al.*⁶ released a corpus designed for direct text-to-query generation with semantic parsing, however given the relative simplicity of generated queries to date compared to the complexity of clinical databases, it's not clear this approach is yet viable for real-world clinical trials recruitment.

In this paper, we present the Leaf Clinical Trials (LCT) corpus. To the best of our knowledge, the LCT corpus is the largest and most comprehensive human-annotated corpus of publicly available clinical trials eligibility criteria. The corpus is designed to accurately capture a wide range of complex, nuanced biomedical phenomena found in eligibility criteria using a rich, granular annotation schema. As the LCT annotation schema is uniquely large, fine-grained and task-oriented, the corpus can serve as a valuable training dataset for NLP approaches while significantly simplifying disambiguation steps and text-processing for query generation. The LCT annotation schema builds upon the foundational work of EliIE¹², an Information Extraction (IE) system for eligibility criteria, and Chia¹⁵, a large corpus of clinical trials of various disease domains. Expanding the EliIE and Chia annotation schemas, we developed the LCT annotation schema to greatly increase the variety of biomedical phenomena captured while also annotating eligibility criteria semantics at a significantly more granular level. Table 1 presents a comparison of the LCT corpus and these corpora.

In the following sections, we (1) discuss the LCT corpus annotation schema, (2) include descriptive statistics on corpus structure, (3) provide baseline named entity recognition and relation extraction performance using the corpus, and (4) discuss areas of future potential for query generation in the Usage Notes section.

Methods

Eligibility criteria and database queries. The NLP tasks involved in transforming eligibility criteria into database queries include **named entity recognition** (NER) to tag meaningful spans of text as named entities, **relation extraction** to classify relations between named entities, **normalization** to map named entities to common coded representations (e.g., ICD-10), **negation detection** to detected negated statements (e.g., “not hypertensive”) and so on. Gold standard corpora quality can thus directly affect performance and the validation of each of these tasks. In this article, we only focus on design and development of the LCT corpus. Figure 1 illustrates why corpora structure and integrity are important for the task of query generation, using examples of eligibility criteria annotated using the LCT annotation schema and corresponding hypothetical Structured Query Language (SQL) queries. In the first eligibility criterion, “pre-eclampsia” is explicitly named, and thus can be directly normalized to an International Classification of Diseases-Tenth Revision (ICD-10) or other coded representation. However, eligibility criteria involving non-specific drugs, conditions, procedures, contraindications, and so on are used frequently in clinical trials. In the second criterion in Fig. 1, “diseases” in “diseases that affect respiratory function” is non-specific, and must be reasoned upon in order to determine appropriate codes, such as asthma,

chronic obstructive pulmonary disease (COPD), or emphysema. Programmatically reasoning to generate queries in such cases would be challenging and often impossible if the underlying semantics were not captured appropriately. With this in mind, we developed the LCT annotation schema in order to enable reasoning and ease query generation for real-world clinical trials use. As the second example in Fig. 1 shows, the LCT annotation captures the semantics of complex criteria, with changes to “respiratory function” annotated using a *Stability[change]* entity and *Stability* relation, and the cause, “diseases” annotated with a *Caused-By* relation. During query generation, a hypothetical algorithm can thus use LCT entities and relations to first normalize the span “respiratory function”, then reason that asthma, COPD, emphysema, and other conditions can affect respiratory function and thus the generated query should find patients with those diagnoses.

Annotation schema. We aimed to develop an expressive, task-oriented annotation schema which could capture a wide range of medical concepts and logical constructs present in eligibility criteria. To accomplish this, we first analyzed previously published corpora^{11,12,15,16} and expanded the list of included biomedical phenomena to fully capture the context and logic present in real clinical trials criteria. As one example, we introduced an entity called *Contraindication* to reflect where use of a given treatment is inadvisable due to possible harm to the patient.

The LCT annotation schema is designed with the following goals and assumptions:

1. The annotation schema should be **practical** and **task-oriented** with a focus on facilitating ease of query generation.
2. A greater number of **more specific, less ambiguous** annotated phenomena should be favored over a smaller number of possibly ambiguous ones.
3. Annotations should be **easily transformable** into composable, interconnected programmatic objects, trees, or node-edge graph representations.
4. The annotation schema should **model eligibility criteria intent and semantics** as closely as possible in order to ensure generated queries can do the same.

The LCT annotation schema is composed of **entities** and **relations**. Entities refer to biomedical, demographic, or other named entities relevant to eligibility criteria, and are annotated as a span of one or more tokens. We organized LCT entities into the following categories:

- **Clinical** - *Allergy, Condition, Condition-Type, Code, Contraindication, Drug, Encounter, Indication, Immunization, Observation, Organism, Specimen, Procedure, Provider.*
- **Demographic** - *Age, Birth, Death, Ethnicity, Family-Member, Language, Life-Stage-And-Gender.*
- **Logical** - *Exception, Negation.*
- **Qualifiers** - *Acuteness, Assertion, Modifier, Polarity, Risk, Severity, Stability.*
- **Temporal and Comparative** - *Criteria-Count, Eq-Comparison* (an abbreviation of “Equality Comparison”), *Eq-Operator, Eq-Temporal-Period, Eq-Temporal-Recency, Eq-Temporal-Unit, Eq-Unit, Eq-Value.*
- **Other** - *Coreference, Insurance, Location, Other, Study.*

The LCT corpus also includes 7 *Name* entities: *Allergy-Name, Condition-Name, Drug-Name, Immunization-Name, Observation-Name, Organism-Name* and *Procedure-Name*. *Name* entities serve a special purpose in the LCT corpus, as they indicate that a span of text refers to a *specific* condition, drug, etc., as opposed to *any* condition or drug. *Name* entities overlap with their respective general entities. For example, the span “preeclampsia” refers to a specific condition, and would thus be annotated as both a *Condition* and *Condition-Name*, while the span “diseases” is non-specific and would be annotated as only *Condition*. A full listing of the LCT annotation guidelines can be found at <https://github.com/uw-bionlp/clinical-trials-gov-annotation/wiki>.

We defined a total of 50 entities in the LCT corpus. Examples of selected representative entities are presented in Table 2. In our representation, a subset of entities have **values** as well. For example, an *Encounter* may have a value of *emergency, outpatient* or *inpatient*. Values are optional in some entities (such as *Encounters* or *Family-Member*, where they may not always be clear or are intentionally broad) and always present in others. In the example annotations presented below, values are denoted using brackets (“[...]”) following entity labels.

Relations serve as semantically meaningful connections between entities, such as when one entity acts upon, is found by, caused by, or related in some way to another. We categorize relations into the following:

- **Alternatives and Examples** - *Abbrev-Of, Equivalent-To, Example-Of.*
- **Clinical** - *Code, Contraindicates, Indication-For, Name, Provider, Specimen, Stage, Type.*
- **Dependent** - *Caused-By, Found-By, Treatment-For, Using.*
- **Logical** - *And, If-Then, Negates, Or.*
- **Qualifier** - *Acuteness, Asserted, Dose, Modifies, Polarity, Risk-For, Severity, Stability.*
- **Temporal and Comparative** - *After, Before, Criteria, Duration, During, Max-Value, Min-Value, Minimum-Count, Numeric-Filter, Operator, Per, Temporal-Period, Temporal-Recency, Temporal-Unit, Temporality, Unit, Value.*
- **Other** - *From, Except, Has, Is-Other, Location, Refers-To, Study-Of.*

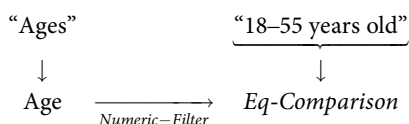
We defined a total of 51 relations in the LCT corpus. Examples of relation criteria are shown in Table 3.

Category	Entity	Values	Example Text
Clinical	Condition	—	Diagnosed with ^{hypertension} _{Condition} in past year
	Contraindication	—	any ^{contraindications} _{Contraindication} to vaginal delivery
	Drug	—	on ^{beta blockers} _{Drug}
	Encounter	emergency, outpatient, inpatient	recently ^{admitted} _{Encounter[inpatient]} to a hospital
	Immunization	—	received ^{Influenza vaccination} _{Immunization}
	Observation	lab, vital, clinical-score, survey, social-habit	^{Platelet count} _{Observation[lab]} less than 500
	Procedure	—	Undergoing or scheduled for a ^{colonoscopy} _{Procedure}
Demographic	Age	—	43 years ^{old} _{Age}
	Birth	—	^{born} _{Birth} within the past 6 months
	Family-Member	mother, father, sibling, etc.	history of ^{maternal} _{Family-Member[mother]} breast cancer
	Language	—	Speaks ^{English} _{Language} or ^{Spanish} _{Language}
Logical	Negation	—	with ^{no} _{Negation} systemic disease
Qualifier	Assertion	intention, hypothetical, possible	which ^{may} _{Assertion[hypothetical]} cause conditions
	Modifier	—	^{alcohol} _{Modifier} or ^{substance} _{Modifier} abuse
	Polarity	low, high, positive, negative	showing ^{elevated} _{Polarity[high]} serum creatinine
	Risk	—	at heightened ^{potential} _{Risk} for suicide
	Severity	mild, moderate, severe	with ^{serious} _{Severity[severe]} complications from surgery
	Stability	stable, change	conditions known to ^{affect} _{Stability[change]} mood
Temporal and Comparative	Criteria-Count	—	at least 3 of ^{the following conditions} _{Criteria-Count} ,
	Eq-Comparison	—	^{greater than 50ml} _{Eq-Comparison}
	Eq-Temporal-Period	past, present, future	^{Active} _{Eq-Temporal-Period[present]} illness
	Eq-Temporal-Recency	first-time, most-recent	^{Latest} _{Eq-Temporal-Recency[most-recent]} BMI > 35
Other	Location	residence, clinic, hospital, unit, emergency-department	Seen at ^{diabetes care clinic} _{Location[clinic]}

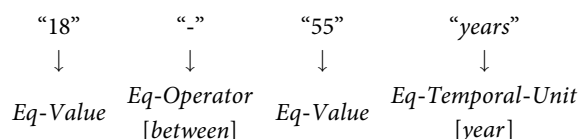
Table 2. Examples of representative LCT annotation schema entities. A full listing of all entities can be found in the LCT annotation guidelines at <https://github.com/uw-bionlp/clinical-trials-gov-annotation/wiki>.

In our annotations, some entity spans overlap with other entity spans in order to fully capture complex underlying semantics. Consider for example, the expression “Ages 18–55 years old”. While an *Age* entity may be assigned to token “Ages”, if an *Eq-Comparison* entity alone were assigned to the span “18–55 years old”, the underlying semantics of the tokens “18”, “-”, “55”, and “years” would be lost. In the following examples, we use the term **fine-grained entity** to refer to entities which are sub-spans of other **general entities**. Fine-grained entities are linked to general entities by relations. We use down arrow symbols (↓) to denote entity annotation and left and right arrow symbols (← and →) to denote relations. The (+) symbols denote overlapping entities on the same span.

The example expression “Ages 18–55 years old” would be annotated in three layers. In the first layer, the expression is annotated with *Age* and *Eq-Comparison* general entities with a relation between them:



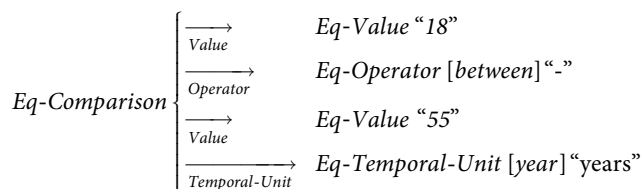
In the second layer, fine-grained entities with respective values are annotated:



Category	Relation	Example Annotation
Alternatives and Examples	Abbrev-Of	Post Concussion Syndrome $\xleftarrow{\text{Condition}}$ $\left(\xrightarrow{\text{Abbrev-Of}} \text{PCS} \xrightarrow{\text{Condition}} \right)$
	Equivalent-To	Thrombocytopenia $\xleftarrow{\text{Condition}}$ $\xrightarrow{\text{Equivalent-To}}$ platelets $\xrightarrow{\text{Observation[lab]}} < 100,000/mm^3$
	Example-Of	skin condition $\xleftarrow{\text{Condition}}$ $\left(\xrightarrow{\text{Example-Of}} \text{e.g.} \xrightarrow{\text{Condition}} \text{eczema} \right)$
Clinical	Contraindicates	conditions $\xrightarrow{\text{Contraindication}}$ $\xrightarrow{\text{Contraindication}}$ MRI $\xrightarrow{\text{Procedure}}$
Dependent	Caused-By	swellings $\xrightarrow{\text{Observation}}$ $\xrightarrow{\text{Caused-By}}$ due to trauma $\xrightarrow{\text{Condition}}$
	Found-By	lesion $\xrightarrow{\text{Observation}}$ $\xrightarrow{\text{Found-By}}$ seen on standard imaging $\xrightarrow{\text{Procedure}}$
	Treatment-For	coronary bypass surgery $\xrightarrow{\text{Procedure}}$ $\xrightarrow{\text{Treatment-For}}$ for atherosclerosis $\xrightarrow{\text{Condition}}$
	Using	total knee arthroplasty $\xrightarrow{\text{Procedure}}$ $\xrightarrow{\text{Using}}$ with spinal anesthesia $\xrightarrow{\text{Procedure}}$
Logical	If-Then	BMI $\xrightarrow{\text{Eq-Comparison}}$ greater than 38 $\xrightarrow{\text{If-Then}}$ for women $\xrightarrow{\text{Life-Stage-And-Gender[female]}}$
Qualifier	Risk-For	risk $\xrightarrow{\text{Risk}}$ $\xrightarrow{\text{Risk-For}}$ of death $\xrightarrow{\text{Death}}$
	Severity	mild $\xrightarrow{\text{Severity[mild]}}$ $\xrightarrow{\text{Severity}}$ symptoms $\xrightarrow{\text{Observation}}$
	Stability	hemodynamically $\xrightarrow{\text{Observation}}$ $\xrightarrow{\text{Stability}}$ unstable $\xrightarrow{\text{Stability[change]}}$
Temporal and Comparative	After	infected $\xrightarrow{\text{Condition}}$ $\xrightarrow{\text{After}}$ following admission $\xrightarrow{\text{Encounter[inpatient]}}$
	Before	diagnosis of aortic stenosis $\xrightarrow{\text{Condition}}$ $\xrightarrow{\text{Before}}$ prior to visit $\xrightarrow{\text{Encounter}}$
	Duration	type 1 diabetes $\xrightarrow{\text{Condition}}$ $\xrightarrow{\text{Duration}}$ for at least 1 year $\xrightarrow{\text{Eq-Comparison}}$
	During	mechanically ventilated $\xrightarrow{\text{Procedure}}$ $\xrightarrow{\text{Duration}}$ while admitted $\xrightarrow{\text{Encounter[inpatient]}}$
	Numeric-Filter	body weight $\xrightarrow{\text{Observation[vital]}}$ $\xrightarrow{\text{Numeric-Filter}}$ less than 110 pounds $\xrightarrow{\text{Eqwithin past 6 monthsComparison}}$
	Minimum-Count	admitted $\xrightarrow{\text{Encounter[inpatient]}}$ $\xrightarrow{\text{Minimum-Count}}$ at least twice $\xrightarrow{\text{Eq-Comparison}}$
Temporality	seen $\xrightarrow{\text{Encounter}}$ $\xrightarrow{\text{Temporality}}$ within past 6 months $\xrightarrow{\text{Eq-Comparison}}$	
Other	Location	admitted $\xrightarrow{\text{Encounter[inpatient]}}$ $\xrightarrow{\text{Location}}$ to the ICU $\xrightarrow{\text{Location[unit]}}$

Table 3. Examples of representative relations. Direction of arrows indicates role, i.e., subject → target entity.

In the third layer, relations connecting fine-grained entities to the general *Eq-Comparison* entity are added:



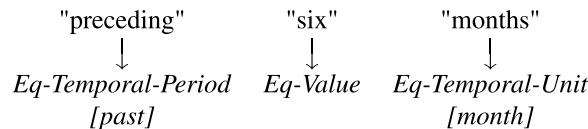
This multilayered annotation strategy allows significant flexibility in capturing entities and relations in a slot-filling fashion, simplifying the task of downstream query generation. We show examples of this in the Usage Notes section.

The LCT annotation schema contributes the following novel features: (1) deep granularity in entities and relations, which enables (2) rich semantic representation, closely capturing the intent of complex clinical trial eligibility criteria and facilitating accurate query generation.

Deep entity and relation granularity. We assume that more specific annotation labels are generally more straightforward to generate accurate queries with. For example, within the span, “preceding six months”, annotating the token “preceding” as *Temporal* (an entity type in Chia) may appear to be adequate, given that an English-speaking human would understand that this refers to the past. Without further information, however, a naive algorithm would be unable to determine (1) whether such an entity refers to the past, present, or future, (2) that the token “six” refers to a numeric value, and (3) that “months” refers to a unit of temporal measurement.

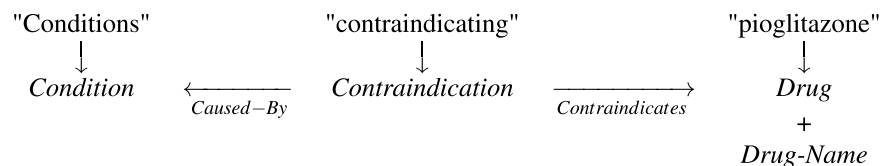
In such cases, most query generation algorithms introduce additional rule-based or syntactic parsing modules, such as SuTime¹⁷ to further normalize the phrase to a value^{4,11}. This ambiguity in label semantics creates unnecessary complexity in downstream systems, requiring that the same text be processed a second time.

In contrast, we designed the LCT annotation schema to favor discrete, explicit entities and relations where possible, with an aim toward reducing the need for additional normalization steps needed for query generation. In our annotation schema, this example would be annotated with the following fine-grained entities:



As shown in the example, each token is uniquely annotated, with the values *[past]* and *[month]* serving to more clearly disambiguate semantics of the temporal phrase to a normalized temporal value. Moreover, as fine-grained entities are connected by relations to general entities, which can in turn have relations to other general entities, the LCT annotation schema is able to capture eligibility criteria semantics at a deeper level than other corpora.

Rich semantic representation. Certain eligibility criteria cannot be directly translated into queries, but instead must first be reasoned upon. For example, a query to find patients meeting the criterion of “conditions contraindicating pioglitazone” requires reasoning to first answer the question, *What conditions contraindicate use of pioglitazone?* Such reasoning may be performed by a knowledge base or other methods, but cannot be done unless the contraindicative relation is detected:



As the span “Conditions” is labeled *Condition* but does not have an overlapping *Condition-Name* entity, it is considered unnamed and thus would need to be reasoned upon to determine. “[P]ioglitazone”, on the other hand, includes a *Drug-Name* entity and is thus considered named. The absence of overlapping *Name* entities serves as an indicator to downstream applications that reasoning may be needed to determine relevant conditions or drugs. We examine additional cases of the LCT’s semantic representation and benefits in the next section, where we compare the LCT annotation schema to Chia’s.

Comparison to Chia. We designed the LCT annotation schema by building upon the important previous work of EliIE and Chia. As Chia itself builds upon EliIE and is more recent, in the next section we compare the LCT corpus and Chia by examining cases of ambiguity handling and annotation difference in entities, relations, and coupling of entity types to the OMOP¹⁸ (Observational Medical Outcomes Partnership) data model. For each case we examine the LCT annotation schema’s novel solutions and contributions. Figure 2 shows comparison examples of annotations of the same eligibility criteria using the two corpora in the Brat annotation tool¹⁹.

Capturing entity semantics. Example 2 of Fig. 2 demonstrates the need to closely capture semantics in clinical trials eligibility criteria for unnamed entities. The span “Medication” in “Medication[s] which affect glyceemic control” refers to *any* drug which potentially affects glyceemic control. As discussed, the LCT annotation schema uses *Name* entities to handle such cases, where the absence in this example of a *Drug-Name* entity indicates that “Medication” refers to any drug, and thus may need to be determined by downstream use of a knowledge base or other methods.

As can be seen, Chia does not differentiate between named and unspecified drugs, conditions, procedures and so on. While it is true that for query generation one may need to normalize these spans to coded representations (e.g., ICD-10, RxNorm or LOINC codes) and may in the process find that the span “Medication” is not a particular medication (and thus can be assumed to be *any* medication), such a workaround nonetheless complicates usage of the corpus in finding and handling such cases in a more direct, less error-prone way.

Consider also the phrase, “after age 30” in example 4 in Fig. 2. In Chia, disambiguation of time units, values, and chronological tense must be performed by additional processing, as the Chia *Value* entity provides no information as to the semantics of the component sub-spans. In contrast, in the LCT corpus the tokens “after”, “age”, “30” are annotated with the explicit entities and relations to enable more straightforward query generation.

Capturing relation semantics. Eligibility criteria frequently contain entities which relate to other entities in the form of examples, abbreviations, equivalencies, or explicit lists. Chia uses *Subsumes* relations to denote that one or more entities are a subset, depend on, or are affected by another entity in some way. In many cases however these entities leave significant semantic ambiguity which may complicate query generation. Consider the phrase:

“conditions predisposing to dysphagia (eg, gastroesophageal reflux disease [GERD] ...)”

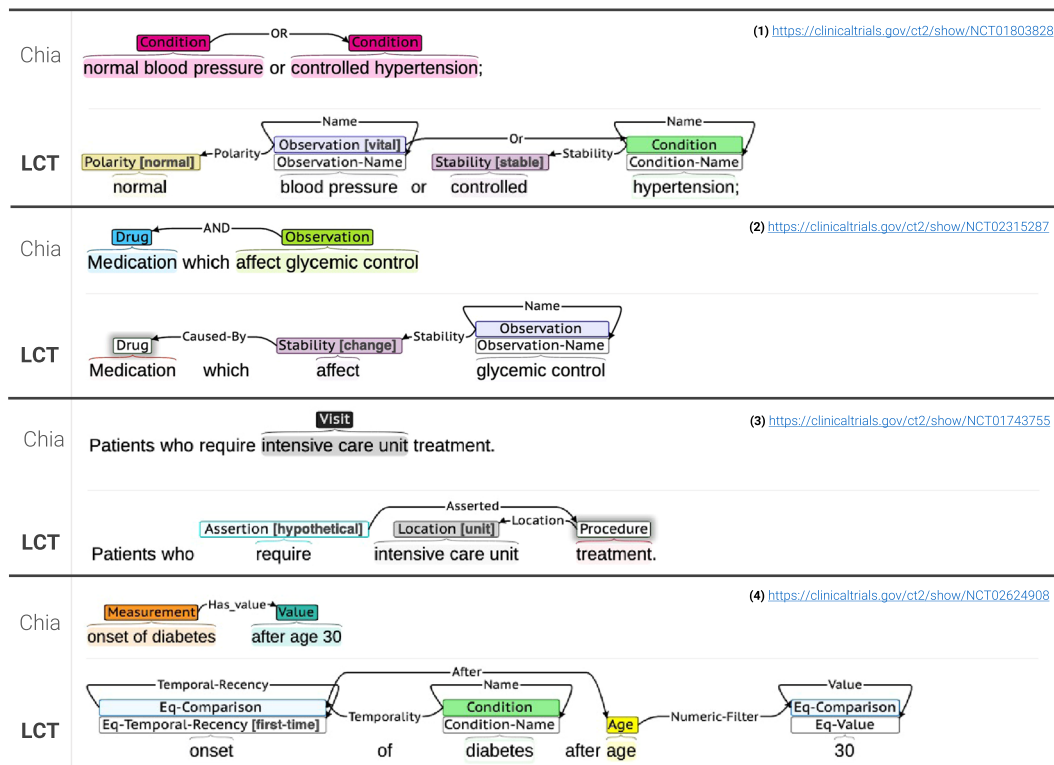
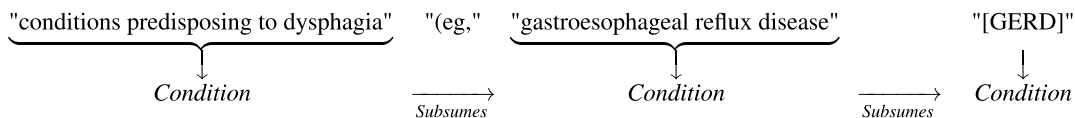
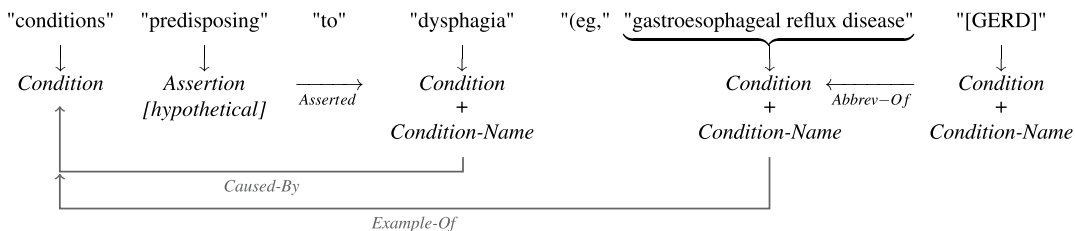


Fig. 2 Examples of clinical trials eligibility criteria annotated with Chia and LCT annotation schemas. Each example shows a criterion from a Chia annotation (above) and an LCT annotation of the same text for purposes of comparison (below).

In this case, “gastroesophageal reflux disease” is an *example* of a condition, while “GERD” is an *abbreviation*. However, both are *Subsumes* relations in the Chia annotation:

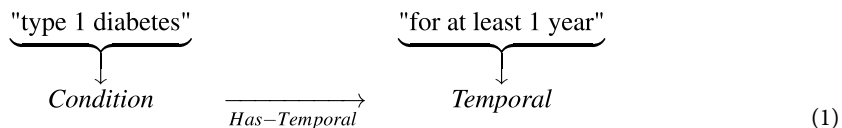


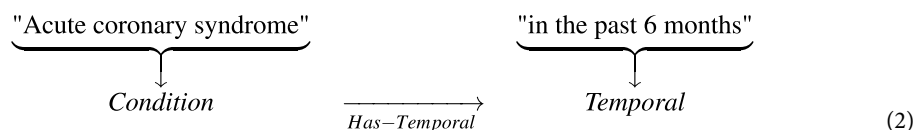
In contrast, in the LCT annotation schema this example would be annotated as:



The LCT annotation uses *Abbrev-Of* and *Example-Of* relations to clearly differentiate relations between “gastroesophageal reflux disease”, “GERD”, and “conditions predisposing to dysphagia”. Additionally, rather than grouping the latter into a single *Condition* entity, the LCT is also much more granular, with the annotation reflecting that dysphagia is a condition patients are hypothetically predisposed to (due to other conditions such as GERD), but not necessarily actively afflicted by.

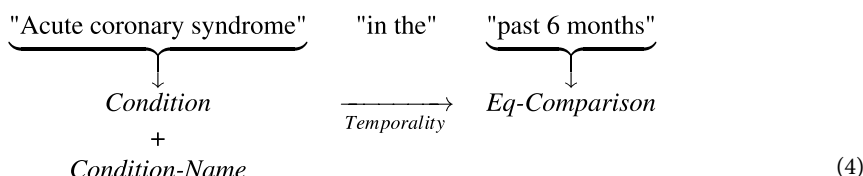
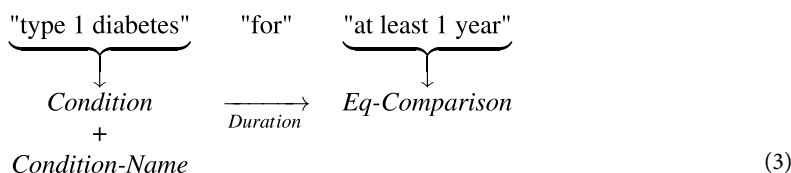
Another example illustrating the importance of capturing relation semantics can be seen in the following Chia annotations:





While syntactically similar, the semantics in chronology expressed in the two criteria are different. In (1), “type 1 diabetes for at least 1 year” suggests that the diagnosis of type 1 diabetes mellitus should have occurred at least 1 year prior to the present. In other words, a unit of temporal measurement (1 year), should have passed since initial diagnosis. In contrast, “Acute coronary syndrome in the past 6 months” (2) suggests that a range of dates between the present and a past event (past 6 months), should have passed since the diagnosis. In Chia, however, the same *Has-Temporal* relation is used for both, blurring distinctions between *durations of time* versus *ranges of dates*, potentially leading to errors during query generation.

In the LCT annotation schema, these would be annotated as (omitting fine-grained entities for brevity):



The LCT annotations distinguish these types of temporal semantics by using distinct *Duration* and *Temporality* relations, allowing downstream queries to more accurately reflect researcher intent. The LCT corpus also does not include “for” or “in the” as part of the entities.

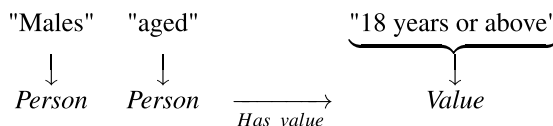
Data model mapping. The Chia annotation schema is mapped to the OMOP Common Data Model¹⁸ and is designed to ease integration with other OMOP-related tools and generation of SQL queries on OMOP databases. Chia OMOP-derived entities generally follow the naming convention of OMOP domains and SQL database tables, such as *Person*, *Condition*, *Device* and so on.

The LCT annotation schema takes a different approach by intentionally avoiding direct mappings to data models. This approach was chosen to (1) allow the annotation entities and relations flexibility to be transformed to any data model (including but not limited to OMOP) and (2) provide flexibility in capturing criteria important to the task of query generation, even when such criteria are not represented in OMOP.

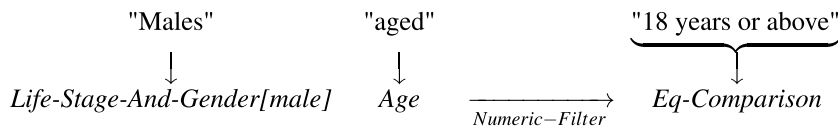
A disadvantage of directly coupling an annotation schema to a data model is evidenced by criteria such as:

“Males aged 18 years and above”

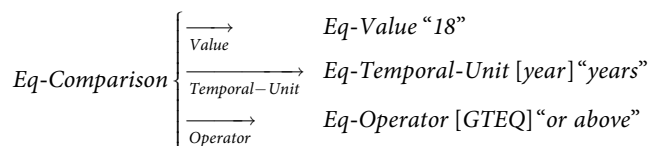
In Chia, spans related to gender and age share the same *Person* entity:



The use of the Chia *Person* entity across gender and age results in loss of information and complications for query generation. As with quantitative and temporal annotations, the generic *Person* entity again forces the burden of normalization and additional parsing to downstream applications. In contrast, this example would be annotated first using general entities and relations in the LCT annotation schema:



Followed by fine-grained entities and values:



The LCT annotation captures the male and age spans as distinguishable entities, closely preserving the semantics of the original text.

Annotation process. We used eligibility criteria from <https://clinicaltrials.gov> as the basis for our corpus.

We extracted 1,020 randomly selected clinical trials eligibility descriptions, 20 for training and inter-annotator comparison and 1,000 for post-training annotation. Documents were included only if they met the following criteria:

1. The combined inclusion and exclusion criteria text was at least 50 characters long.
2. The clinical trial was uploaded on or after January 1st, 2018. This date was chosen because we found that clinical trials performed further in the past appeared to exhibit less structural consistency in language, punctuation and indentation compared to more recent text.

During annotation, 14 documents were found to be information poor (often with no spans to annotate) and discarded, resulting in 1,006 total annotated eligibility descriptions. Annotation was performed by two annotators, the first a biomedical informatician and the second a computer scientist. For initial annotation training, 20 documents were distributed to both annotators. Annotation was done in the following steps:

1. Annotation meetings were held bi-weekly for 3 months following initial annotation training in which the annotation guidelines were introduced. Initial meetings focused on discussion of annotation guideline implementation and revision. After each meeting, the annotation guidelines were revised to include new named entities and relationships and inter-annotator agreement was recalculated using F1-scores. Each annotator used the UMLS Terminology Services (UTS) Metathesaurus Browser (<https://uts.nlm.nih.gov/uts/umls/home>) to search for biomedical concepts whose meaning was unclear.
2. After annotation guideline revisions and annotation training were completed, eligibility criteria were assigned to each annotator, with each clinical trial eligibility criteria annotated by a single annotator using the BRAT annotation tool¹⁹. Due to differences in time availability for annotation, roughly 90% (887 documents) of the annotation task was performed by the first annotator, and 99 documents by the second annotator.
3. At the point in which 50% of the corpus was annotated, we trained two neural networks (one for general entities and another for fine-grained entities) using the NeuroNER tool²⁰ on our manually annotated eligibility criteria to predict annotations for the remaining 50%. NeuroNER is a state-of-the-art entity extraction system which has been successfully adapted to tasks such as de-identification and concept extraction. NeuroNER utilizes bidirectional Long Short-Term Memory and Conditional Random Fields (biLSTM + CRF) for token-level multiple-label prediction. We used the NeuroNER-predicted entities to auto-populate our remaining eligibility descriptions.
4. Manual annotation was completed on the remaining 50% of eligibility descriptions by editing and correcting the predicted entities from NeuroNER in (3).

The resulting corpus included 887 single-annotated and 119 double-annotated total notes.

Data Records

The LCT corpus annotated eligibility criteria and text documents can be found at <https://doi.org/10.6084/m9.figshare.17209610>²¹. Code for pre-annotation and analysis are available at <https://github.com/uw-bionlp/clinical-trials-gov-data>. The LCT corpus is annotated using the Brat “standoff” format. The Brat format includes two file types, “.txt” files and “.ann” files.

Text (.txt) files. The free-text eligibility criteria information in the 1,006 documents of the LCT corpus. Each file is named using the “NCT” identifier used by <https://clinicaltrials.gov>.

Annotation (.ann) files. The annotation files used by Brat for tracking annotated spans of text and relations. Each .ann file corresponds to a .txt file of the same name. Each row of a .ann file may begin with a “T” (for an entity) or “R” (for a relation), followed by an incremental number for uniquely identifying the entity or relation (e.g., “T15”). “T” rows are of the form “T<number> <entity type> <start character index> <stop character index>”, where start and stop indices correspond to text in the associated .txt file. “R” rows are of the form “R<number> <relation type> Arg1: <ID> Arg2: <ID>”, where ID values correspond to identifiers of entities. Additionally, for ease of annotation certain LCT relations are defined as arguments of Brat “events”, identified by “E”. “E” rows are of the form “E<number> <entity type>: <ID> <relation type>: <ID>”.

More information on the Brat format can be found at <https://brat.nlplab.org/standoff.html>.

Technical Validation

Inter-annotator agreement. Inter-annotator agreement was calculated using F1 scoring for entities and relations with 20 double-annotated documents. Entity annotations were considered matching only if entity types and token start and end indices matched exactly. Relations annotations were similarly considered matching only if relation type and token start and end indices of both the subject and target matched exactly.

Initial inter-annotator agreement using the 20 training documents was 76.1% for entities and 60.3% for relations. Inter-annotator agreement improved slightly to 78.1% (+2%) for entities and 60.9% (+0.6%) for relations in the 99 additional double-annotated documents, indicating reasonably high annotator agreement considering the complexity of the annotation task.

Task	Architecture	Hyperparameter/Embeddings	Training Value
Named Entity Recognition	biLSTM + CRF	Character Dimensions	25
		Token Embedding Dimensions	100
		Learning Rate	0.005
		Dropout	0.5
		Pretrained Embeddings	GloVe ²⁸
Relation Extraction	BERT & R-BERT	Pretrained Model	SciBert
		Learning Rate	0.00003

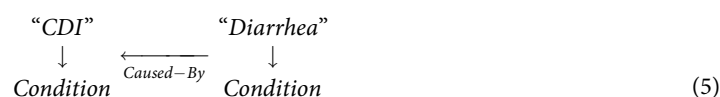
Table 4. Hyperparameters and pre-trained embeddings used for named entity recognition and relation extraction baseline results. For the NER task, the same architecture and hyperparameters were used for both general and fine-grained entity models. For the relation extraction task, the same hyperparameters were used with both the BERT and R-BERT architectures.

We found two categories of annotation differences in double-annotated eligibility criteria. First, in spans such as:

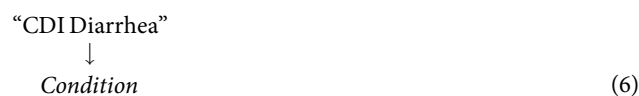
“Reported being a daily smoker”

While both annotators tended to annotate “smoker” as both a *Condition* and *Condition-Name*, adjectives such as “daily” were often annotated as *Eq-Comparison* and *Eq-Temporal-Unit[day]* by one annotator and *Stability[stable]* by the other. After review, these were generally reconciled to the first pattern.

The second category of differences can be seen in spans such as “CDI Diarrhea”, where “CDI” refers to Clostridium Difficile Infection. In these cases, the annotators may annotate this span as (omitting *Condition-Name* entities for brevity):



or



The first annotation separates “CDI” and “Diarrhea” into two entities, with “Diarrhea” *Caused-By* “CDI”, while the second annotation treats them as a single entity. Reconciliation in these cases was done by referring to the UMLS Metathesaurus to determine whether the combined span existed as a single concept within the UMLS. As “Clostridium Difficile Diarrhea” exists as a UMLS concept (C0235952), the annotations in this example were reconciled to use the second, multi-span entity.

Baseline prediction. To evaluate baseline predictive performance on the LCT corpus, we first created a randomly assigned 80/20 split of the corpus, with 804 documents used for the training set and 202 for the test set. For entity prediction, we trained NER models using biLSTM + CRF and BERT²² neural architectures. For BERT-based prediction, we used two pretrained models trained on published medical texts, SciBERT²³ and PubMedBERT²⁴. For both biLSTM + CRF and BERT predictions, we trained one model to predict general entities and another for fine-grained entities.

For relation extraction, we evaluated SciBERT for sequence classification as well as a modified BERT architecture, R-BERT, following methods developed by Wu & He²⁵, also using the pretrained SciBERT model. Table 4 shows hyperparameters used for each task.

We achieved the highest micro-averaged F1 score of 81.3% on entities using SciBERT and 85.2% on relations using the R-BERT architecture with SciBERT. Results of representative entities and relations are shown in Tables 5 and 6.

Among entities, we found two particular categories performed relatively well with F1 scores of 70% or often greater: (1) Entities which are syntactically varied but occurred relatively frequently in eligibility descriptions, such as *Condition*, *Procedure*, and *Eq-Comparison*, (2) Entities which sometimes occurred less frequently but with greater relative syntactic consistency and structure, such as *Age*, *Contraindication*, and *Birth*. Entities which occurred very infrequently, such as *Death* tended to have both low precision and recall.

For relations, we found the most frequently occurring relations, such as *Eq-Comparison*, *Temporality*, *Modifies*, and *Example-Of* to perform well, with F1 scores greater than 85%. Among less frequently occurring relations, we found a number of cases where relations which tend to occur in similar positions within sentences and grammatical structures were frequently mistaken during prediction. For example, *Eq-Comparison* (e.g., “greater than 40”) and *Minimum-Count* (e.g., “at least twice”) were sometimes incorrectly predicted. We found similar incorrect predictions for relations such as *Treatment-For* (e.g., “Surgery for malignant pathology”) and *Using* (e.g., “knee joint replacement with general anaesthesia”).

In future work we intend to examine approaches improving prediction of less frequently occurring entities and relations. A full listing of baseline prediction results can be found with the annotation guidelines at <https://github.com/uw-bionlp/clinical-trials-gov-annotation/wiki/Named-Entity-Recognition-and-Relation-Extraction-performance>.

Category	Entity	Count	biLSTM + CRF	PubMedBERT	SciBERT
Clinical	Condition	7,087	78.6/78.1/78.3	76.1/79.4/77.7	78.4/83.3/80.8
	Contraindication	142	93.7/78.9/85.7	77.4/80.0/78.6	100.0/96.6/98.3
	Drug	1,404	76.8/81.3/79.0	74.1/80.9/77.4	73.4/80.9/77.0
	Encounter	302	64.1/58.1/60.9	51.7/61.7/56.3	58.3/74.4/65.4
	Observation	2,558	74.3/66.1/69.9	67.9/73.5/70.6	72.1/77.6/74.7
	Procedure	3,016	68.4/75.5/71.9	67.0/75.9/71.2	71.3/79.4/75.1
Demographic	Age	708	91.3/95.4/93.3	82.4/88.5/85.3	99.1/98.3/98.7
	Birth	27	100.0/80.0/88.8	100.0/62.5/76.9	100.0/62.5/76.9
	Death	35	33.3/33.3/33.3	0.0/0.0/0.0	100.0/20.0/33.3
	Family-Member	147	40.0/19.0/25.8	33.3/55.5/41.6	44.9/61.1/51.7
	Language	194	92.5/96.1/94.3	73.8/100.0/84.9	96.6/93.5/95.0
Logical	Negation	952	74.3/82.7/78.2	60.9/73.1/66.4	73.5/82.9/77.9
Qualifier	Assertion	1,157	66.6/62.8/64.7	56.1/58.9/57.5	62.1/65.8/63.9
	Modifier	3,464	65.0/58.3/61.5	59.2/64.0/61.5	58.5/65.4/61.8
	Polarity	360	82.5/88.0/85.1	74.6/67.4/70.8	81.4/79.5/80.4
	Risk	117	93.1/96.4/94.7	91.3/91.3/91.3	95.4/91.3/93.3
	Severity	569	86.8/90.8/88.7	76.7/79.5/78.1	86.5/94.1/90.2
	Stability	397	84.2/67.6/75.0	79.4/75.0/77.1	75.3/84.7/79.7
Temporal and Comparative	Criteria-Count	33	50.0/66.6/57.1	28.5/40.0/33.3	12.5/20.0/15.5
	Eq-Comparison	5,298	83.1/83.8/83.4	81.4/85.0/83.2	85.3/89.3/87.3
	Eq-Temporal-Period	2,057	88.7/89.2/88.9	70.0/73.9/71.9	82.6/86.3/84.4
	Eq-Temporal-Recency	131	68.7/84.6/75.8	43.4/55.5/48.7	50.0/66.6/57.1
	Eq-Temporal-Unit	1,808	95.1/97.6/96.4	97.4/98.1/97.8	98.2/99.4/98.8
	Eq-Value	3,835	91.8/95.3/93.5	95.5/96.2/95.9	96.4/97.1/96.7
Other	Location	371	68.5/58.7/63.2	65.4/71.6/68.3	73.4/78.3/75.8
—	Total	56,146	80.2/79.6/79.9	75.3/78.7/77.0	79.0/83.7/81.3

Table 5. Baseline entity prediction scores (% Precision/Recall/F₁). Corpus-level micro-averaged scores are shown in the bottom row. For brevity a representative sample of entities is shown. *Count* refers to the total count of unique spans annotated in the entire corpus. Entities included in the total count and scores but omitted for brevity are *Acuteness, Allergy, Condition-Type, Code, Coreference, Ethnicity, Eq-Operator, Eq-Unit, Indication, Immunization, Insurance, Life-Stage-And-Gender, Organism, Other, Specimen, Study and Provider*.

Annotation quality evaluation. To determine the quality of single-annotated documents compared to those which were double-annotated, we trained NER models (one for general and another for fine-grained entities, as in earlier experiments) using SciBERT with the 887 single-annotated documents and evaluated on the 119 double-annotated documents. The results were a precision of 79.7%, recall of 82.5%, and an F1 score of 81.4%, which are very close to the highest performance of our randomly split train/test set results shown in Table 5. These results indicate relative uniformity and consistency in the corpus across both single- and double-annotated documents.

As the latter near-half (493 documents) of the LCT corpus was automatically annotated, then manually corrected, we also evaluated the quality of the manually annotated portion versus the semi-automatically annotated portion to ensure consistency. We first trained NER models with SciBERT using the manually annotated portion and tested on the semi-automated portion, then reversed the experiment and trained on the semi-automated portion and tested on the manually annotated portion. Results are shown in Table 7.

Results of the experiments when training on both the manually and semi-automatically annotated halves of the corpus show comparable results, with the greatest difference being in precision, with the manual annotation-trained model performing slightly worse (−4.7%) in prediction versus the semi-automated annotation-trained model. Overall F1 scores were similar at 78.6% and 80.0%, suggesting reasonable consistency across the corpus.

Usage Notes

The LCT corpus is designed to facilitate query generation and question answering for real-world clinical trials and clinical research, specifically for a future version of the Leaf cohort discovery tool². Figure 4 visualizes an example of a transformation of LCT annotated data into a Directed Acyclical Graph (DAG) structure, which can then be potentially compiled into SQL, FHIR, SPARQL, or other query methods.

To demonstrate the value and utility of the corpus, using the trained baseline Named Entity Recognition and Relation Extraction models, we developed a simple prototype web application to test named entity and relation prediction on unseen text. Figure 3 shows a screenshot of the models correctly predicting entities and relations on an input sentence not present in the LCT corpus. As can be seen, the models are able to predict entities and relations with very high accuracy on new text, demonstrating the power of the corpus.

Category	Relation	Count	SciBERT	R-BERT + SciBERT
Alternatives and Examples	Abbrev-Of	462	95.2/90.9/93.0	92.3/93.1/94.2
	Equivalent-To	516	61.5/69.5/65.3	59.6/67.3/63.2
	Example-Of	1,497	94.8/92.9/93.8	90.5/91.7/91.1
Clinical	Contraindicates	153	90.9/90.9/90.9	90.9/90.9/90.9
	Caused-By	726	63.0/86.4/72.9	78.6/86.4/82.3
	Found-By	293	90.4/59.3/71.7	9.3/71.8/75.4
	Treatment-For	457	69.2/69.2/69.2	61.7/74.3/67.4
	Using	405	73.8/83.7/78.4	66.6/64.8/65.7
Logical	And	821	54.1/60.0/56.9	53.8/53.8/53.8
	If-Then	261	57.6/65.2/61.2	55.5/65.2/60.0
	Negates	984	74.3/91.0/81.8	74.5/88.7/81.0
	Or	4,156	85.1/93.2/89.0	88.4/92.2/90.2
Qualifier	Asserted	1,184	83.7/89.0/86.3	85.9/89.0/87.5
	Modifies	3,400	90.9/94.2/92.5	92.2/95.4/93.8
	Risk-For	90	92.3/85.7/88.8	92.8/92.8/92.8
	Severity	529	80.2/96.6/87.6	86.3/96.6/91.2
	Stability	395	76.0/92.6/83.5	76.4/95.1/84.7
Temporal and Comparative	After	166	75.0/70.5/72.7	72.2/76.4/74.2
	Before	320	70.2/86.6/77.6	78.1/83.3/80.6
	Duration	243	59.3/79.1/67.8	64.5/83.3/72.7
	During	350	66.6/68.7/67.6	63.6/65.6/64.6
	Numeric-Filter	1,957	84.6/93.3/88.7	85.7/92.3/88.8
	Minimum-Count	173	64.2/69.2/66.7	71.4/76.9/74.0
	Temporality	2,645	80.7/90.7/85.4	81.8/92.2/86.7
Other	Location	207	64.2/94.7/76.6	69.2/94.7/80.0
—	Total	24,379	80.2/88.2/84.0	82.5/88.0/85.2

Table 6. Baseline relation prediction scores (% Precision/Recall/F₁). Corpus-level micro-averaged scores are shown in the bottom row. For brevity a representative sample of relations is shown. *Count* refers to the total count annotated in the entire corpus, including relations not shown. The count total excludes general to fine-grained entity relations, which as overlapping spans are not used for relation prediction. Relations included in the total count and scores but omitted for brevity are *Acuteness, Code, Criteria, Except, From, Indication-For, Is-Other, Max-Value, Min-Value, Polarity, Provider, Refers-To, Specimen, Stage, Study-Of and Type*.

Training Set	Test Set	Precision	Recall	F1
Manual	Semi-automated	75.4	82.1	78.6
Semi-automated	Manual	80.1	79.9	80.0

Table 7. Results of NER experiments using the manually annotated and semi-automated portions of the corpus. The manually annotated portion includes 513 documents while the semi-automatically annotated portion is 493 documents.

Limitations. The LCT corpus is designed as a granular and robust resource of annotated eligibility criteria to enable models for entity and relation prediction as means of query generation. The corpus does have a number of limitations however which should be recognized. First, the corpus is largely singly annotated, with 119 of 1,006 documents (11%) double annotated and reconciled, while double annotation is generally considered to be the gold standard in the NLP research community. As discussed in the Technical Validation section, the reasonably high F1 score from experiments to evaluate NER when training on the singly annotated portion of the corpus suggests relative consistency of annotation across both single and double annotated documents. Additionally, entities in roughly half of the LCT corpus (493 documents) were automatically predicted, then manually corrected. This can potentially lead to data bias if predicted entities are not thoroughly reviewed and corrected by human annotators. Similar results from our experiments to detect differences in performance by training on the manually annotated portion versus the semi-automatically annotated portion (F1 scores of 78.6% and 80.0%) suggest this may not be not a significant issue. Last, though the ultimate goal of the LCT corpus is to facilitate more accurate query generation, the corpus itself is not composed of queries by which it can be compared to similar corpora and thus cannot necessarily be proven to be more effective. Similarly, as we do not formally define a quantifiable means for measuring semantic representation within annotations, it is difficult to demonstrate that the LCT corpus enables more accurate query generation.

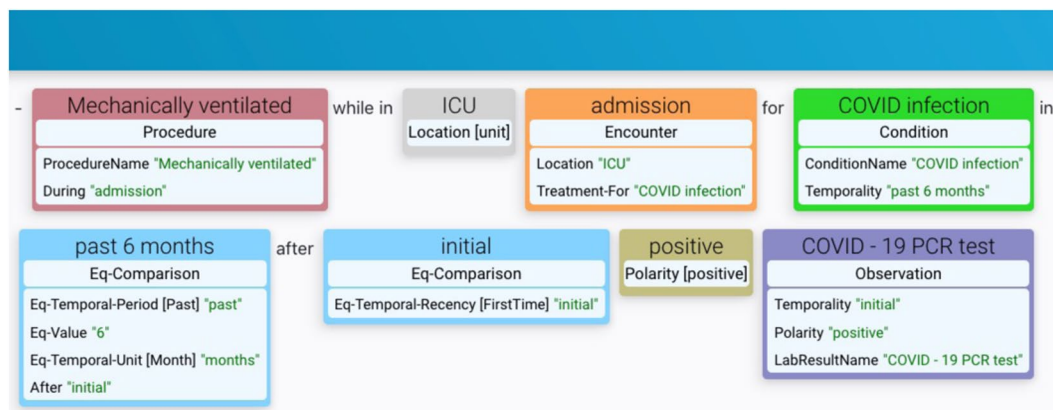


Fig. 3 Screenshot of a prototype web application for real-time entity and relation prediction on custom user input text.

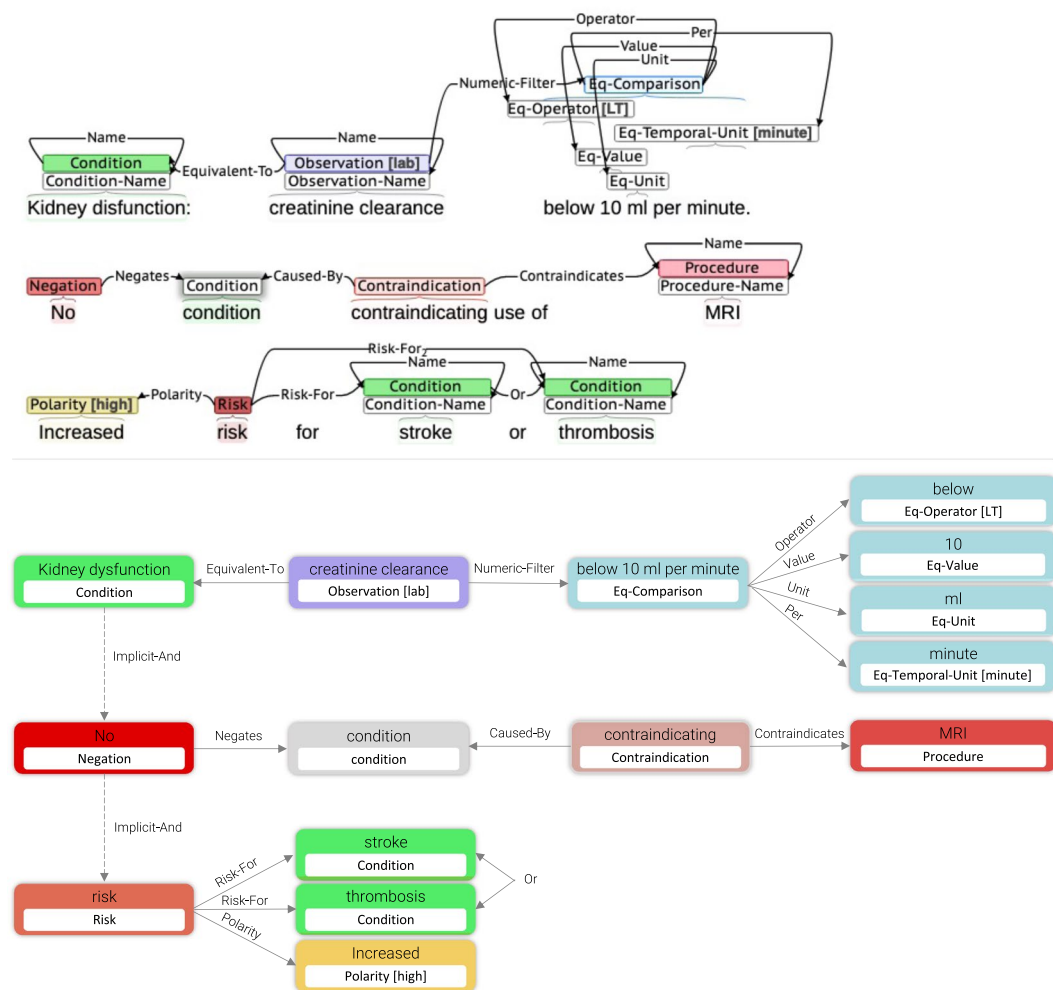


Fig. 4 Example of an LCT annotated document (top) transformed into a Directed Acyclical Graph (bottom). LCT entities and relations are readily transformable into tree, graph, or object-oriented representations used for query generation.

Future work. As discussed, evaluation of generated query accuracy and semantic representation in annotations is difficult and can potentially be done by different methods, such as ROUGE scoring²⁶ to compare generated query syntax to expected syntax, or by including UMLS Concept identifiers²⁷ within the LCT annotation schema and comparing the number of UMLS concepts to those found in other corpora.

Taking a different approach, in future work, we intend to evaluate the LCT corpus and query generation methods by evaluating generated queries in the context of real clinical trials which have taken place at the University of Washington (UW). As the UW EHR system maintains clinical trial enrollments and patient identifiers alongside clinical data, it is possible to query our EHR databases to compare patients who actually enrolled in clinical trials versus those found by our queries had they been run at the time of a given trial. We believe this means of evaluation is uniquely valuable as it uses real world clinical trials and EHR data while scoring queries by the accuracy of their ultimate results rather than less consequential factors such as syntax.

Code availability

All code used to generate, pre-annotate, and analyze the LCT corpus is freely available at <https://github.com/uw-bionlp/clinical-trials-gov-data>. The LCT annotation guidelines can be found at <https://github.com/uw-bionlp/clinical-trials-gov-annotation/wiki>.

Received: 1 February 2022; Accepted: 28 June 2022;

Published online: 11 August 2022

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Acknowledgements

This study was supported in part by the National Library of Medicine under Award Number R15LM013209 and by the National Center for Advancing Translational Sciences of National Institutes of Health under Award Number UL1TR002319. Experiments were run on computational resources generously provided by the UW Department of Radiology.

Author contributions

N.D. created the annotation guidelines, was primary annotator, and drafted the original manuscript. T.M. served as secondary annotator and reviewed and revised the manuscript. O.U. reviewed the task and goals as well as reviewed and revised the manuscript. M.Y. conceived of the annotation task, supervised, and reviewed and revised the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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