NLPMEDTERM CORPUS ANNOTATION GUIDELINE

English version

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1. ANNOTATION CRITERIA

The task consists in annotating 8 types of entities on Spanish texts from journal abstracts about clinical trial studies, published in the SciELO repository, and clinical trial annoucements from EudraCT. The entities belong to semantic groups from the Unified Medical Language System® (UMLS) (Bodenreider 2004) referring to:

- Anatomic entities (ANAT)
- Biochemical or pharmacological substances (CHEM)
- Medical devices (DEVI)
- Pathologic conditions (DISO)
- Genes and genetic material (GENE)
- Living beings and virus (LIVB)
- Physiological processes (PHYS)
- Lab tests, diagnostic or therapeutic procedures (PROC).

I addition, 5 types of temporal entities were annotated based on the TimeML scheme adapted to the clinical domain (Styler et al. 2014):

- Age entities: this class was not used in TimeML, but was needed for the task
- Date: e.g. 2022
- Duration (also called *set* in the TimeML scheme): e.g. 2 horas ('2 hours')
- Frequency: *mensualmente* ('monthly')
- Time or part of the day: e.g. por la noche ('at night')

The following types of medication information entities were marked:

- Contraindicated: e.g. contraindicación a aspirina ('contraindication to aspirin')
- Dose or strength: e.g. 150 mg
- Form: e.g. *gel, pastillas* ('pills')
- Route or administration mode: e.g. oral

Lastly, assertion and uncertainty information was annotated:

- Negation cue (Neg cue) and Negated events: e.g. sin fiebre ('no fever')
- Speculation cue (Spec_cue) and Speculated events: e.g. *posible carcinoma* ('possible carcinoma')

To check the type of entity or to understand each concept mention, the following sources are recommended:

- CIMA (Centro de información online de medicamentos): https://cima.aemps.es
- International Clasification of Diseases vs. 10 (ICD-10), Spanish version, electronic edition (3^a ed, 2010), Ministerio de Sanidad, Consumo y Bienestar Social: https://eciemaps.mscbs.gob.es/ecieMaps/browser/index 10 mc.html
- Dictionary of Medical Abbreviations SEDOM: http://www.sedom.es/diccionario/

¹ www.scielo.org

² www.clinicaltrialsregister.eu

- DrugBank: https://www.drugbank.ca
- MedlinePlus: https://medlineplus.gov/spanish/
- UMLS Metathesaurus Browser (requires a free register as a user): https://uts.nlm.nih.gov//metathesaurus.html
- Vademecum: https://www.vademecum.es/
- Wikipedia



Figure 1. Sample of the annotation

The goals of the annotation are **detecting** entities, as mencioned in the scientific literature or clinical texts, and also **normalize** the entities to the corresponding medical concepts. Consequently, some annotation criteria were defined considering whether the potential annotation could be mapped to concepts or codes in standard terminologies in the UMLS Metathesaurus. We have especially followed the International Classification of Diseases vs 10 (ICD-10).

SCOPE OF THE ANNOTATION

In general, annotate full phrases if possible:

(1.) el **episodio hemorrágico** (S1130-01082008000800004) Annotate *episodio hemorrágico* (DISO) and not only *hemorrágico*.

We do not annotate articles and cardinal numbers (*dos, tres...*), nor punctuation marks (comma, dot...) at the begnining and the end of the entity. E.g. annotate *episodio hemorrágico* and not *el episodio* hemorrágico; or *eventos adversos* (not *147 eventos adversos*; the semicolon is not annotated either):

(2.) reportaron 147 **eventos adversos**; tuvieron alguna relación causal 13,6% Annotate only *eventos adversos* (DISO) (S1729-519X2016000600017)

The start or end of the annotacion cannot overlap with the beginning or the end of other annotation; only some entities are completely allowed inside other entity (see Section Annotation of nested entities):

(3.) DO NOT ANNOTATE: administración de vacunas vivas (2018-002521-30)

ANNOTATE: [administración] de [vacunas vivas]

administración (PROC) and vacunas vivas (CHEM)

Only the more specific entitites will be annotated, including modifiers expressing medical concepts, adjacent to the medical term:

(4.) carcinoma renal metastásico (S0004-06142006000100006) Annotate carcinoma renal metastásico as DISO, and not carcinoma renal.

Try to annotate the more specific entity (the wider span):

(5.) el **déficit de calcitriol** DISO (0211-699500012698) Annotate *déficit de calcitriol*, not only *déficit*.

If annotating an adjective or modifier is unclear, check the scope of the term in a terminological resource (e.g. ICD-10 or UMLS Metathesaurus). A list of common modifiers to be annotated (or not) are included in Appendix 1. **Modifiers expressing general concepts are not annotated**: e.g. *distinto, futuro, próximo, siguiente* (excepting full entities registered in the UMLS: see list in Appendix):

(6.) **hipertensión** futura DISO (S0025-76802004000500002) Annotate only *hipertensión*.

(7.) diferentes **fármacos** CHEM (S0034-70942013000300003) Annotate only *fármacos*.

(8.) miembros superiores ANAT (\$0034-70942013000300004) Annotate miembros superiores (UMLS CUI: C1140618)

In some contexts, derivational adjectives expressing a medical concept are annotated, isolated from the head term (although this might not be annotated). These cases are annotated only **to avoid missing unannotated information**:

- (9.) acompañada de mejoría **endoscópica** (S0025-76802004000500002) Annotate *endoscópica* (PROC), but not *mejoría endoscópica*.
- (10.) fue llevado a cabo en una sala <u>quirúrgica</u> ortopédica. En total, 60 pacientes ASA I-III seleccionados para **artoplastia electiva total de rodilla** fueron incluidos (S0034-70942012000300003) Do not annotate *quirúrgica* because we already annotate *artroplastia electiva total de rodilla* (PROC)
- (11.) El inicio del efecto <u>anestésico</u> fue más corto después de aplicar la **técnica** alveolar media (S0213-12852017000100005)
 Do not annotate *anestésico* because we already annotate *técnica alveolar media* (PROC)

Very long noun phrases are not annotated, but only the **head of the phrase with its modifiers (not several prepositional groups)**:

(12.) Estudio comparativo del uso de mitomicina C en el pterigium recidivante (\$0864-21762008000200004)

Annotate estudio comparativo as PROC, mitomicina C as CHEM, and pterigium recidivante as DISO

In entities of type procedure (PROC), the prepositional phrase is annotated or not according to the need for understanding the context, or if the full term is found in a reference terminology. **Annotating very long terms is discouraged**. In general:

- Terms with the prepositional phrase are annotated if an UMLS CUI exists, or if they can be mapped to a category from the International Classification of Diseases v.10:
 - (13.) dos días antes de la cirugía de terceros molares (S0034-70942012000400003)

Annotate as PROC *cirugía de terceros molares* (C0577760 Surgical removal of third molar tooth)

- (14.) **examen en lámpara de hendidura** (\$0365-66912010000400002) Annotate the full entity as PROC (\$C0419360 Slit lamp biomicroscopy)
- (15.) mediante procedimiento quirúrgico de citorreducción

(S0009-741115002339)

Annotate procedimiento quirúrgico de citorreducción (one entity) as PROC (C3850079 Cytoreductive Surgery)

(16.) La **prevención de <u>diabetes</u>** y sus complicaciones es un desafío (S0104-11692012000300008)

Annotate prevención de diabetes (C1659987 Diabetes prevention), diabetes (DISO) and complicaciones (DISO)

- (17.) el **control de la hipertensión intracraneal** (S1130-14732005000100001) Annotate *control de la hipertensión intracraneal* as PROC (C0150260 Intracranial Pressure Monitoring)
- Annotate the full term with the prepositional phrase if it helps to understand the meaning of the text; e.g., in entities of type procedure (PROC), each term might distinguish the *Intervention* from the *Comparator*:
 - (18.) Grupo I (n = 75): **funduplicatura de 360°**, **corta y holgada por laparoscopia** en el Hospital Universitario Dr. Peset de Valencia. -Grupo II (n = 28): **funduplicatura 360°**, **corta y holgada por vía abierta** (S1130-01082005000500005)

 Annotate PROC in *funduplicatura de 360°*, *corta y holgada por laparoscopia* (Intervention), and in *funduplicatura de 360°*, *corta y holgada por vía abierta* (Comparator).

In cases different from the above, annotate each term of type PROC and annotate another entity in the term introduced by preposition (e.g. <u>anestesia</u> con, <u>analgesia</u> con, <u>cirugía</u> en, <u>tratamiento</u> de, <u>prevención</u> de, <u>control</u> de, etc.). Terms introduced by prepositions tend to refer to a different concept. If in doubt, each term is annotated separately if the full term lacks a category or code in the ICD-10 or UMLS MetaThesaurus:

(19.) Tratamiento de la anorexia en hemodiálisis

(S2254-28842013000500055)

Annotate separately Tratamiento (PROC), anorexia (DISO), hemodiálisis (PROC)

(20.) analgesia epidural posquirúrgica con bupivacaína

(S0121-07932008000600004)

Annotate separately analgesia epidural (PROC) and bupivacaina (CHEM)

- (21.) Cirugía de la enfermedad por reflujo gastroesofágico
 - Annotate cirugía (PROC) and enfermedad por reflujo gastroesofágico (DISO). (S1130-01082005000500005)
- (22.) **tratamiento** del **pterigium recidivante** (S0864-21762008000200004) Annotate *tratamiento* (PROC) and *pterigium recidivante* (DISO).
- (23.) aplicación de microcorriente como tratamiento en las úlceras venosas (S0104-11692012000400016)

Annotate aplicación de microcorriente (PROC, C2147192, microcurrent electrical stimulation), tratamiento (PROC), úlceras venosas (DISO) and venosas (ANAT)

(24.) **prevención** de **fenómenos embólicos** (S0066-782X2010001600013) Annotate *prevención* (PROC) and *fenómenos embólicos* (DISO)

We tend to annotate in the same entity a general or underspecified term adjacent to a specific term from the same semantic type (introduced by preposition):

- (25.) la cicatrización mediante **terapia con VAC** (S0009-741115002911) Annotate as PROC *terapia con VAC* ('cierre asistido por vacío', C1956080 Vacuum-Assisted Closure); do not annotate *terapia* and *VAC* separately.
- (26.) **cirugía de revascularización coronaria** (S0025-76802017000100001) Annotate one entity, and not *cirugía* and *revascularización coronaria* separately.

When 2 head terms can be annotated with the same label, only annotate one (that with the shorter span):

(27.) aplicación de una técnica de energía muscular

Annotate técnica de energía muscular (PROC) and not aplicación de una técnica de energía muscular (S1134-80462010000700004)

Likewise, regarding mentions of pathologies (DISO), each entity is annotated separately, provided that each one can be mapped to a different UMLS concept and the full combination of mentions lacks a CUI or they are different ICD-10 categories:

(28.) pacientes obesos con nefropatías proteinúricas

(S0211-69952009000500007)

Annotate 2 DISO entities: obesos (ICD-10: E66.9) and nefropatías proteinúricas

On the contrary, the full mention is annotated in the same entity if there is an ICD-10 category or a concept in the UMLS:

(29.) pacientes con carcinoma diferenciado de tiroides con metástasis ganglionares cervicales (S0009-741115002261)

Annotate from carcinoma to cervicales, because a specific concept exists in

Annotate from *carcinoma* to *cervicales*, because a specific concept exists in UMLS (C2981270).

(30.) hiperparatiroidismo secundario de la insuficiencia renal

Annotate one DISO entity (C0271847; Hyperparathyroidism due to renal insufficiency; ICD-10: N25.81)

Similarly, we tend to annotate in the same entity those mentions with terms sintomas/signos/manifestaciones de + pathology (DISO):

(31.) **síntomas de depresión** (S0104-11692016000100416) Annotate one DISO entity (C0086132 Depressive Symptoms).

Long terms with coordinated or juxtaposed noun phrases may be ambiguous to parse; non-head phrases might be interpreted as modified or not by the head term. In this case, we annotate only the shortest entity (independent from the head term):

(32.) Se evaluaron diariamente los **síntomas de infección respiratoria**, **diarrea aguda** y **efectos secundarios** (S0120-41572014000100011)
Annotate 3 DISO entities: *síntomas de infección respiratoria, diarrea, efectos secundarios* (do not annotate one full, long DISO entity).

We annotate in the same way entities referring to an anatomical concept. We annotate the full mention if there is a CUI in the UMLS, or if annotating the full entity is needed to understand the text content and distinguish the most specific entity. Otherwise, we annotate each term separately:

(33.) área de corte de la capa de fibras nerviosas de la retina

(\$0365-66912007000700004)

Annotate one ANAT entity (C0229219 Structure of nerve fiber layer of retina) rather than two independent entities (*capa de fibras nerviosas, retina*)

(34.) **fibras del músculo** del **ventrículo izquierdo** (S0066782X2010001600011) Annotate 2 ANAT entities: *fibras del músculo* (C0242697 Muscle Fibers) and *ventrículo izquierdo* (C0225897 Left ventricular structure)

Regarding entities expressing the type of clinical trial, we annotate the full mention (criteria are detailed in the Section explaining the annotation of PROC entities):

(35.) Estudio clínico prospectivo fase IV abierto y sin grupo control (S0716-10182019000100032)

(36.) estudio fase IV no aleatorizado

(S0716-10182019000100032)

Brand names of drugs are annotated only if they are mapped to an UMLS CUI or if they appear in CIMA, UMLS or DrugBank. Do not annotate the ® or TM characters:

(37.) los nuevos sellantes adhesivos, como **Tissucol**®

Do not annotate ®, but only *Tissucol*, as CHEM (S0009-741115002261)

(38.) dieta-formula normocalórica e hiperproteica (<u>Vegestart complet</u>®) Do not annotate *Vegestart complet* (not in UMLS or CIMA) (\$0212-16112010000600008)

As an exception, the ® character is annotated if it occurs in the middle of a multiword term (to avoid discontinuous annotations):

(39.) evaluar si el Quantiferon® TB-gold In Tube (QFT-GIT) puede contribuir (S0211-69952011000200009)
Annotate Quantiferon® TB-gold (CHEM, C1875713 QUANTIFERON-TB GOLD) inside Quantiferon® TB-gold In Tube (PROC); also, annotate PROC in the abbreviation (QFT-GIT)

We annotated the terms after the hyphen in mentions with *pre-* or *post-* prefixes (or similar ones). Only the most frequent occurrences reported in the medical literature (*pre-anaesthesia*, *post-surgical*...) are annotated as full temporal entities (with the *pre/post-* prefix):

(40.) post-**CPRE** (S1130-01082017000300002)
Annotate PROC in *CPRE* ('colangiopancreatografía retrógrada endoscópica')

(41.) PMB (presión máxima basal) pre-tratamiento

(S1130-01082004001200006)

Annotate PROC in *PMB*, presión máxima basal y tratamiento; and also annotate Time in pre-tratamiento.

(42.) sin-CEC vs. con-CEC (S0025-76802017000100001) Annotate CEC ('circulación extracorpórea') as PROC

ANNOTATION OF NESTED ENTITIES

Entities included in other entities with a wider scope will be anotated, provided that both do not have the same semantic group. For example, in the following context, the inner entities *nervio óptico* or *cadera* (ANAT) **will not be annotated** inside the wider entitity *cabeza del nervio óptico* or *músculos abductores de la cadera* (also ANAT):

(43.) cabeza del **nervio óptico** ANAT (\$0365-66912007000700004)

(44.) músculos abductores de la <u>cadera</u> ANAT (\$0325-00752016000600009)

Examples of nested entities to be annotated:

(45.) <u>transaminasas hepáticas</u> se conservaron en rangos normales (S0716-10182019000100032)

Annotate transaminasas hepáticas (PROC), transaminasas (CHEM), hepáticas (ANAT)

(46.) medición de **glucosa** (S0212-16112011000300017) Annotate *glucosa* (CHEM) inside *medición de glucosa* (PROC)

(47.) **hallux** valgus (S2306-41022015000200007) Annotate *hallux* (ANAT) inside *hallux valgus* (DISO).

(48.) toxinas **urémicas** (S0211-69952013000700005) Annotate *urémicas* (DISO) inside *toxinas urémicas* (CHEM)

Inner entities incorrectly pre-annotated are to be deleted: e.g. *indice* (ANAT) in *Índice* de masa corporal.

When overlap occurs, nested entities cannot belong to two different entities with a wider span. Inner entities can only belong to one or another entity with a wider span, but not to two different ones. For example, in this context:

(49.) DO NOT ANNOTATE: cierre con sutura de la herida (\$0009-741115002911)

ANNOTATE: [cierre con sutura] de la [herida]

Two annotations are possible: *cierre con sutura* (PROC) or *sutura de la herida* (PROC). However, annotations overlapping across different entities are discouraged, thus we annotate *cierre con sutura* (PROC) and *herida* (*DISO*).

ANOTATION OF COORDINATED ENTITIES

In some contexts, coordinated or juxtaposed terms, or enumerations, need to be included in the same annotated entity, provided that they occur in the same sentence. Several entities are not annotated if occurring across sentences, or if they include too many words (e. g., more than 10).

(50.) **artroplastia de cadera o rodilla** (2018-002465-18) Annotate one PROC entity (C0086511 Knee Replacement Arthroplasty; C0186193 Arthroplasty of hip)

Annotate in one entity coordinated mentions with *y/o*:

(51.) la incidencia de **náuseas y/o vómitos** (S1134-80462016000200002) Annotate one DISO entity (C0027498 Nausea and vomiting)

However, in some contexts it is not possible to annotate the full mention (e.g. because several words or noisy items appear). A solution can be annotating only the common head word, or the most general term:

(52.) AlJ: 5 tenían la forma pauciarticular; 9, la poliarticular y 6, la sistémica. (S0034-75312010000100001)

Annotate only as DISO *AIJ* ('artritis idiopática juvenil', C1444845, Juvenile idiopathic arthritis)

In some contexts, part of the entity is elliptic (very often, with words such as *versus* or *vs*). To avoid annotating mentions that could not be generalized, only the full entity is annotated (the modifier of the elliptic word is not marked). We will consider the fact that the full, non-elliptic entity can be annotated in other context of the same text:

(53.) Calidad de vida de pacientes con cáncer de próstata en tratamiento con bloqueo androgénico continuo vs intermitente: estudio prospectivo (...) Fundamento: El tratamiento con bloqueo androgénico intermitente (BAI) pretende mejorar la calidad de vida. (S1137-66272015000200003) Annotate cáncer de próstata (DISO), bloqueo androgénico continuo (PROC) y bloqueo androgénico intermitente (PROC). It is not necessary to annotate vs intermitente, because the entity referring to that concept is annotated elsewhere in the text.

In the case of PROC entities that express a measurement or analitic procedure, two (or more) different entities are annotated when occurring in coordinated or juxtaposed structures:

(54.) Tomamos datos de **niveles de hemoglobina** y **albúmina** (S0212-16112016000200036)

Annotate two PROC entities (*niveles de hemoglobina*; *albúmina*), but not only one entity

SPELLING AND TYPOGRAPHICAL ERRORS

Entities with spelling, typographical and tokenization errors are **also annotated**, although they do not follow the academic or normative use:

(55.) náusea y vomito **post operatorio** (S0066-782X2011000300008) Annotate DISO, although the normative forms are *postoperatorio* o *posoperatorio*

We did not annotate abreviations with spelling errors, which are not common in the research community and cannot be generalized to other contexts (e.g. *EICA* instead of *IECA*).

ABBREVIATIONS AND ACRONYMS

Abbreviations and acronyms of medical entities are also annotated:

(56.) diabéticos tipo 2 (**DM2**) (S0212-16112017000300532) Annotate *diabéticos tipo* 2 and acronym *DM2* as DISO

(57.) con índice de masa corporal (**IMC**) de 30,7 (S0211-69952012000200010) Annotate as PROC *índice de masa corporal* and *IMC*

We also annotate English abbreviations and acronyms, even though they are not translated or adapted to Spanish:

```
(58.) marcadores de inflamación (PCR, PAI-1, TNF-alpha ... Annotate PCR, PAI-1 and TNF-alpha (S0212-16112014001200013)
```

Do not annotate one-letter acronyms or abbreviations: e.g. *P* (standing for 'phosphorus') is not annotated.

Abbreviations specifying biological entities are annotated: e.g. entities referring to lymphocytes (ANAT), biochemical receptors (CHEM), etc.

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(59.) linfocitos TCD4 ANAT (S0716-10182019000100032)
```

Abbreviations are annotated as full words. Parts of a given word will not be annotated, although they are abbreviations:

```
(60.) saturación periférica de oxígeno (SpO2) (S0716-10182019000100032) Annotate SpO2 (PROC), not O2.
```

Abbreviations and acronyms of proper names are not annotated:

```
(61.) consumieron dos fórmulas en cuatro ocasiones (Glucerna <u>SR</u>(r) Laboratorios Abbott <u>C.A</u> [FG] y Enterex Diabetic(r), Victus, <u>C.A</u> [FE] Do not annotate SR, C.A, FG or FE. (S0212-16112017000300532)
```

Spelling errors in abbreviations are not annotated:

```
(62.) el grupo tratado con EICA (...) pacientes inicialmente tratados con IECA Annotate only IECA (CHEM), but not EICA (0211-699505018925)
```

Abbreviations/acronyms are not annotated if they are not commonly used in the scientific litterature. We do not annotate them when they are used as *ad-hoc* anaphoras to shorten a text. We recommend looking up abbreviations/acronyms in resources such as SEDOM (www.sedom.es/diccionario/), or checking their frequency in publications available at Google Books or Google Scholar (see list in Appendix).

```
(63.) solución glucosada (SG) In this context, SG is annotated because it is registered in SEDOM.
```

(64.) Se incluyeron a 30 pacientes, 14 en el grupo arterial (\underline{GA}), 10 en el grupo venoso (\underline{GV}) (S0066-782X2009001000010) In this context, we do not annotate abbreviations because they are just used in this text, they are not widespread in the scientific literature.

When an abbreviation or acronym to be annotated occurs in the middle of a multiword term, the full entity is marked:

(65.) la enfermedad de Crohn (EC) fistulosa (S1130-01082004000800004)

Annotate as DISO enfermedad de Crohn (EC) fistulosa (C3888864 Fistulising Crohn's disease)

If the abbreviation occurs at the end of the full term, it is annotated separately:

(66.) el **umbral de dolor a la presión (UDP)** (S1134-80462010000700004) Annotate as PROC 2 mentions: *umbral de dolor a la presión* and *UDP*

NEGATED ENTITIES

Entities occurring in negated contexts are also annotated, and the negation cue is marked as *Neg_cue*. Unlike other corpora (e.g. Vincze et al. 2008; Lima et al. 2020), the full scope is not marked; only the event or negated concept is marked with the attribute Negated:

(67.) 301 <u>no</u> vacunados (S1131-57682003000400010) Annotate vacunados (PROC) with attribute Negated; and *no* as Neg cue

(68.) <u>sin</u> complicaciones clínicas DISO (S1729-519X2016000500004) Annotate *sin* (Neg_cue) and *complicaciones clínicas* (DISO, Negated)

(69.) <u>no</u> hubieran recibido **tratamiento antibiótico**(S1022-51292011000400003)
Annotate *no* (Neg cue) and *tratamiento antibiótico* (DISO, Negated)

In cases of lexical negation (e.g. asymptomatic) only the Negated attribute is marked:

(70.) Treinta y cinco sujetos asintomáticos

With *ninguno/a(s)*, the negation is marked in the noun, the event or both:

- (71.) **ninguno falleció** o comenzó **hemodiálisis** (S1729-519X2013000300020) Annotate *ninguno* (Neg_cue), *falleció* (DISO, Negated) and *hemodiálisis* (PROC, Negated)
- (72.) **ningún paciente** con **efectos secundarios** (S0120-41572006000500020) Annotate *ningún* (Neg_cue), *paciente* (LIVB, Negated) and *efectos secundarios* (DISO, Negated)

In negated coordinated contexts (e.g. *no... ni...*), only annotate the negation cue that is syntactically closer to the negated entity:

(73.) no se observaron cambios en variables antropométricas **ni efectos adversos** (S0212-16112014001200013) Annotate *ni* (Neg_cue) and *efectos adversos* (DISO [Negated])

(74.) sin evidencia clínica ni de laboratorio de infección

(S1022-51292011000400003)

Annotate *ni* (Neg cue) and *infección* (DISO [Negated])

Negation is not marked in elliptic entities:

(75.) Se formaron 2 grupos: en los que se utilizó **Tissucol® (**grupo caso) y en los que <u>no</u> (grupo control) (S0009-741115002261)

Do not annotate negation, only *Tissucol* (CHEM, without atttribute Negated).

(76.) 94 **pacientes** fueron evaluados para su elegibilidad, de los cuales 54 fueron <u>excluidos</u> (S0009-741115002261)

Do not annotate negation, only *pacientes* (LIVB, without atttribute Negated).

In laboratory tests results, *negativo* ('negative', modifier) might indicate a negative value with regard to a **pathology or medical condition**: in this case, the adjective should be marked as Neg_cue, and the event as Negated. However, it is not annotated (nor the Negated attribute in the entity referring to the test or procedure) if the context could be interpreted as a procedure not conducted:

(77.) test de embarazo negativo en sangre u orina

(S1022-51292011000400003)

Annotate *negativo* (Neg_cue) referred to *embarazo* (PHYS [Negated]); *test de embarazo* (PROC) is annotated, without attribute Negated.

(78.) Cultivo de orina negativo al inicio del estudio

(S1022-51292011000400003)

Annotate only *cultivo de orina* (PROC); *negativo* is not Neg cue

Do not annotate negation in doubly negated contexts that can be interpreted as a positive statement:

(79.) sin excluir a ningún paciente

(\$0210-48062010000300010)

Do not annotate negation (only *paciente*, LIVB); the sentence is interpreted as: 'all patients were included'.

(80.) <u>ninguna</u> necesidad de vasoactivos (<u>excepto dopamina <5µg/kg/</u>)

(S0210-56912010000700003)

Only annotate *ninguna* (Neg_cue) and Negated in vasoactivos (CHEM). Do not annotate *excepto* as Neg cue nor the attribute Negated in *dopamina* (CHEM)

ENTITIES EXPRESSING SPECULATION

We annotate as Spec_cue ('Speculation cue') those words introducing uncertain or probable events, outward circumstance or risk (e.g. pathologies or medical conditions). The full scope is not marked; the attribute Speculated in only marked on the focus (event or concept: CHEM, DISO, LIVB, PROC...):

(81.) puede mejorar los resultados y minimizar los posibles efectos indeseables

Annotate *posible* (Spec_cue) and *efectos indeseables* (DISO, Speculated).(S0212-16112010000600008)

(82.) <u>podría</u> ser útil para la <u>prevención</u> (S0025-76802004000500002) Annotate *podría* (Spec cue) and *prevención* (PROC [Speculated]).

Speculated or Spec_cue are not marked in other modality expressions not expressing uncertainty (e.g. *es necesario*, 'it is necessary'):

(83.) ¿es necesaria la supresión ácida máxima para disminuir el resangrado? (S1130-01082008000800004)

Do not annotate Spec cue; only annotate ácida (CHEM) and resangrado (DISO)

(84.) El uso de **morfina intratecal** es una <u>opción terapéutica</u> segura (S1130-01082008000800004) Do not annotate Spec_cue in *opción terapéutica*; only annotate *morfina intratecal*

We mark Spec_cue and Speculated in contexts expressing both uncertainty and negation:

(CHEM)

(85.) <u>pueden o no</u> acompañarse de **neutropenia** (S0370-41062002000100005) Annotate *pueden o no* (Spec cue) and *neutropenia* (DISO, [Speculated])

Conditional subordinate clauses (*si, en caso de que...* + verbo) express condition or hypothesis and are not marked with speculated information:

(86.) la **cirugía** mejora la **AV**, siendo más efectiva <u>si</u> se asocia <u>ICG</u> (S0365-66912006001000005)
Annotate only *ICG* (CHEM), *cirugía* (PROC) and AV (C0200150, Visual acuity testing, PROC)

From a linguistic perspective, we annotate contexts corresponding to the epistemic modality, which expresses "the degree of probability of the state of affairs according to the knowledge of the speaker" (Herrero Zorita, 2017:41). We do not annotate as Speculated those contexts where *poder* ('can') expresses a capacity or a real possibility (not uncertain nor speculated):

- (101.) La Ropivacaína se puede utilizar cómo anestésico local (S0210-1238201324) ('ropivacaine can be used as como local anesthetic)
- (102.) Los pacientes pueden dar su consentimiento informado ('patients have the capacity to give their informed consent')

Ambiguous contexts (i.e. can express deontic modality or speculation) will not be annotated.

ENTITIES EXPRESSING MEDICAL HISTORY

The attribute History_of is annotated in entities expressing past medical conditions (DISO) or procedures (PROC); i.e. entities that are not necessarily present at the moment of the writing of the text or the participation in the clinical trial:

(87.) La **hiperglucemia** sin antecedentes previos de **diabetes mellitus (DM)** (S0212-16112015000500025)

Annotate *hiperglucemia* (DISO), *diabetes mellitus* (DISO, with attributes Negated and History of) and *DM* (DISO, [Negated][History of])

- (88.) Haber recibido cualquier tipo de **vacunación** (2018-000497-30) Annotate *vacunación* (PROC) with attribute History of
- (89.) Pacientes que hayan recibido un **tratamiento** previo (2016-004441-82) Annotate *tratamiento* (PROC) with attribute History_of
- (90.) Antecedente de **cirugía ocular** (2017-000250-19) Annotate *cirugía ocular* (PROC) with History of; annotate also *ocular* (ANAT)
- (91.) Alergia o intolerancia conocida al producto de investigación (2020-001379-34)

Annotate alergia and intolerancia (both DISO) with attribute History_of; annotate also producto de investigación (CHEM).

(92.) **seguimiento** en un **estudio clínico** previo (2016-004365-16) Annotate *estudio clínico* (PROC) with attribute History_of; annotate also *seguimiento* (PROC).

In general, History_of is marked only in contexts introduced by words such as antecedentes, historia de, previo, anterior... In case of doubt, do not annotate anything (including when the procedure or the patology might happen in the future):

(93.) sufre una **reacción adversa** durante los estudios M16-067 o M16-065 (2016-004676-22)

Annotate *reacción adversa* as DISO, without History_of; it is unclear if the adverse event occurred in the pasr or might occur in a future study.

We both mark the attributes History_of and Negated in contexts indicating the absence of any medical history:

(94.) Pacientes sin **tratamiento** previo (2018-001423-40) Annotate *tratamiento* (PROC) with attributes History_of and Negated; *Pacientes* (LIVB) is also annotated

Likewise, History of can be annotated with the Speculated attribute:

(95.) Historia <u>sospechada</u> o conocida de **tuberculosis** (2020-001162-12) Annotate *tuberculosis* (DISO) with attributes History of and Speculated

Entities expressing family history medical conditions are annotated with the attribute Family history of:

(96.) Antecedentes familiares de **enfermedad de Alzheimer** (2017-004454-42) Annotate *enfermedad de Alzheimer* (DISO) with attribute Family_history_of

In disjunctive concepts, both attributes (Family_history_of and History_of) can be marked:

(97.) Antecedentes personales o familiares de **carcinoma medular de tiroides**(2012-004413-14)
Annotate DISO with attributes History_of and Family_history_of

CONTRAINDICATIONS

Pharmacological entities (CHEM) or procedures (PROC) are marked with the attribute Contraindicated, generally when introduced with words such as contraindicado, contraindicación, etc.:

- (98.) <u>contraindicación</u> conocida a **corticoesteroides** (2020-001278-31) Annotate *corticoesteroides* (CHEM, attribute Contraindicated)
- (99.) Pacientes con <u>contraindicación</u> para **anestesia espinal** (2017-001430-25) Annotate *pacientes* (LIVB) and *anestesia espinal* (PROC, Contraindicated)

Contraindicated is also marked in other PROC or CHEM entities introduced by words or expressions implying that the use of the medication is not recommended (e.g. because it would be harmful to the patient):

(100.) Enfermedades que <u>limiten</u> el uso de **ibuprofeno** y/o **paracetamol** (2019-000902-31)
Annotate CHEM in *ibuprofeno* and *paracetamol* with attribute Contraindicated

(101.) Uso de **medicación** <u>prohibida</u> en el estudio (2014-005419-18) Annotate <u>medicación</u> (PROC) with attribute Contraindicated

ENTITIES EXPRESSING ASPECT

In the current version, we do not annotate entities expressing recurrence or relapse; these terms tend to be classified as Findings in the UMLS Metathesaurus:

(102.) Hubo 2 casos (3,8%) de <u>recurrencia</u> de **coagulopatía**Annotate only *coagulopatía* as DISO (S0121-07932007000300002)

(103.) La duración del **tratamiento** disminuyó el número de <u>recaídas</u> (S1665-11462016000500309) Do not annotate *recaídas*, only *tratamiento* (PROC)

(104.) Analizamos las <u>recidivas</u> de la **pancreatitis** (S1137-66272003000300004) Annotate only *pancreatitis* as DISO.

We only annotate these types of terms in multiword entities that cannot be split up (e.g. recurrencias isquémicas, recidivas tumorales) or if there is an ICD-10 class:

```
(105.) pacientes adultos con mieloma múltiple recidivante (2017-001465-24) (C2349261 Relapse multiple myeloma, ICD-10: C90.02)
```

```
(106.) portadores de pterigium recidivante (S0864-21762008000200004) (C0155158 Recurrent pterygium, ICD-10: H11.069)
```

```
(107.) Aborto recurrente (2017-001878-42) (C0000809 Recurrent abortion; ICD-10: N96)
```

FOREIGN WORDS

Entities adapted straigthaway from English, without being translated to Spanish, are also annotated:

```
(108.) Se realizó bypass gástrico en 54 pacientes...
Annotate bypass gástrico as PROC (S0212-16112006000800002)
```

In contexts where both the Spanish and the foreign word occur, we only annotate the Spanish term and the abbreviation:

```
(109.) realizar una queratoplastia endotelial de membrana de Descemet (DMEK: Descemet membrane endothelial keratoplasty) (S0365-66912009000500004)
```

Annotate *queratoplastia endotelial de membrana de Descemet* and *DMEK* both as PROC; do not annotate *Descemet membrane endothelial keratoplasty.*

ANAPHORIC ENTITIES

Do not annotate pronouns, determiners or adjectives expressing a referential meaning with regard to another entity:

```
(110.) uso adecuado de betabloqueantes o intolerantes a <u>ellos</u>
(S0066-782X2010001600003)

Annotate only betabloqueantes (CHEM) and intolerantes (DISO)

(111.) una técnica útil en el tratamiento de <u>dichas</u> fracturas
(S1130-05582017000300143)
```

Annotate tratamiento (PROC) and fracturas (DISO)

2. ANNOTATED ENTITIES

We annotate entities corresponding to a subset of semantic groups from the Unified Medical Language System (UMLS) (Bodenreider 2004); namely the following ones:

- ANAT (anatomic entities)
- CHEM (pharmaco-chemical entities)
- DEVI (medical devices)
- DISO (pathological conditions)
- GENE (genes and genetic material)
- LIVB (living beings and virus)
- PHYS (physiological processes)
- PROC (procedures)

We chose this subset of semantic groups since they fit more adequately the type of data annotated (abstracts of clinical trials studies and trial protocols announcements).

ANAT

Entities expressing parts of the body. We include here entities from the following UMLS semantic types:

- Anatomical Structure: e.g. cisura
- Body Location or Region: e.g. epigastrio
- Body Part Organ or Organ Component: e.g. músculo
- Body Space or Junction: e.g. muñeca
- Body Substance: e.g. sangre
- Body System: e.g. sistema urinario
- Cell Component: e.g. neurotúbulo
- Cell: e.g. basófilo
- Embryonic Structure: e.g. neuroectodermo
- Fully Formed Anatomical Structure: e.g. cuerpo
- Tissue: e.g. tejido nervioso

Examples:

(112.) La permanencia fue mayor en la pierna (\$0325-00752018000100041)

(113.) en la insuficiencia **renal** crónica (0211-699504017174)

(114.) contaminación con **heces** (S0210-48062010000300010)

Some anatomic entities follow words such as *región, porción, cabeza...,* or *primer, segundo,* etc. We include all terms in the annotetion whenever an UMLS concept exists:

(115.) puntuación para cada **región del colon** (S1022-51292016000400002) Annotate *región del colon* (C0447522 Region of colon)

(116.) anestesia troncular de **10 dedo** (S0210-1238201324) Annotate *10 dedo*

CHEM

We include here entities from the following UMLS semantic types:

- Amino Acid, Peptide, or Protein: e.g. serina
- Antibiotic: e.g. penicilina
- Biologically Active Substance: e.g. factor I, neurotransmisor
- Carbohydrates
- Chemical: e.g. ozono
- Chemical Viewed Functionally: e.g. odorante
- Chemical Viewed Structurally: e.g. isopropilo
- Clinical Drug: e.g. tacrólimus
- Element, Ion, or Isotope: e.g. carbono
- Enzyme: e.g. lipasa
- Hazardous or Poisonous Substance: e.g. cianuro
- Hormone: e.g. progesterona
- Immunologic Factor: e.g. vacuna nonavalente
- Indicator, Reagent, or Diagnostic Aid: e.g. eluyente
- Inorganic Chemical: e.g. fosfato
- Nucleic Acid, Nucleoside, or Nucleotide: e.g. ADN
- Organic Chemical: e.g. carbonato, ácido graso
- Pharmacological Substance: e.g. opioide
- Receptor: e.g. receptor de la progesterona
- Vitamin: e.g. retinol

Examples:

(117.) mantenimiento con adalimumab	(S1130-01082008001100002)
(118.) pacientes que reciben acetato cálcico	(0211-699500012698)
(119.) no recibían ácido fólico ni vitamina B6	(0211-699501013259)

We annotate together compound chemical and pharmacological entities expressing a standard pharmacological preparation, or referring to compounds that do not exist separately:

```
(120.) amoxicilina-clavulánico (S0210-4806200600090000)
Annotate in one entity (UMLS C0054066, Amoxicillin / Clavulanate)
```

On the contrary, we annotate separately 2 CHEM entities in contexts where the entities do not refer to a mixture or substance preparation:

```
(121.) Varfarina o aspirina en la prevención de fenómenos embólicos (S0066-782X2010001600013)
```

Biochemical substances or elements (e.g. calcio, fósforo, bicarbonato) might be ambiguous in contexts where the chemical substance can also be interpreted as

laboratory analysis (e.g. when lab results are reported). E.g. *calcio:* 8,8 ± 0,5 mg/dl. Annotation criteria are explained in Section 2 (Criteria regarding ambiguities)

DEVI

Entities referring to medical instruments or devices:

```
(122.) El UDP se midió, por medio de un <u>algómetro analógico</u>
Annotate algómetro analógico (S1134-80462010000700004)
```

These types of entities can be part of a larger PROC entity: colocar una sonda ('probe placement'), alimentación por sonda ('probe feeding')...

(123.) garantiza la óptima **colocación del <u>catéter</u>** (S0211-69952010000300014) Annotate *colocación del catéter* as PROC; and *catéter* as DEVI.

```
(124.) post extracción de <u>sonda</u> (S0004-06142008000700005) Annotate extracción de sonda as PROC; and sonda as DEVI.
```

Note the difference in the annotation: verbs such as *sondar*, *sondaje*, *o cateterizar* are anotated PROC (procedures using a medical device such as a probe or catheter); however, *sonda* ('probe') is annotated as DEVI.

The scope of the annotation of DEVI entities might cause doubts; terminological resources (e.g. UMLS) will be used to annotate the wider scope, as registered in a thesaurus. Models, brand or registered names will not be annotated if no CUI exists:

```
(125.) Una sonda nasogástrica 20 F fue insertada
Annotate sonda nasogástrica (C0085678) but not sonda nasogástrica 20 F (the full entity is not registered in the UMLS). (S0212-16112011000100009)
```

When an entity can be interpreted as a procedure (PROC) or a medical device (DEVI), we prioritized annotating PROC:

```
(126.) evaluar el uso sistemático de enemas (S1022-51292011000400003) Annotate enemas as PROC and not DEVI
```

DISO

We include here entities from the following UMLS semantic types:

- Acquired Abnormality: e.g. callo
- Anatomical Abnormality: e.g. arruga
- Cell or Molecular Dysfunction: e.g. gen mutado
- Congenital Abnormality: e.g. dismorfia
- Disease or Syndrome: e.g. diabetes
- Experimental Model of Disease: e.g. sarcoma de rous

- Injury or Poisoning: e.g. traumatismo
- Mental or Behavioural Dysfunction: e.g. bulimia nerviosa
- Pathologic Function: e.g. shock alérgico
- Neoplastic Process: e.g. tumor
- Sign or Symptom: e.g. fiebre

Examples:

(127.) adalimumab en la **enfermedad de Crohn** (S1130-01082008001100002)

(128.) pacientes **hipertensos** con **diabetes tipo 2** y **albuminuria** (0211-699501013956)

(129.) los **signos y síntomas de depresión** se evaluaron (S0104-11692016000100416)

Annotate in the same span *signos y síntomas de depresión* (C4716638 Signs and symptoms of depression)

In the current version, severity degrees of pathologies are only annotated if an ICD-10 category exists:

(130.) Indicación pública: **miastenia grave** (2013-003589-15) Annotate *miastenia grave* (C0026896 Myasthenia Gravis; ICD-10: G70.0)

(131.) **deterioro cognitivo leve** (2015-004238-85) (C1270972 Mild cognitive impairment; ICD-10: G31.84)

As an exception, in order to get more generalizable annotations, we do not annotate intermediate stages or degrees of the chronic kidney disease, which are often expressed in ranges or inexact values:

(132.) **ERC** estadio 3A-4 (S1134-009615002090) Annotate only *ERC* (C1561643 Chronic Kidney Disease, ICD-10. N18), even though more specific ICD-10 categories exist (N18.3 and N18.4)

(133.) **Insuficiencia renal** >3B Annotate only *Insuficiencia renal*

Regarding entities with a severity modifier without an ICD-10 category, only the pathologic entity is annotated (not the modifier):

(134.) 72,3% fueron de **laceración** <u>de primer grado</u> (S0104-11692008000300007) Annotate only *laceración* (C0043246 Laceration).

(135.) 61% de los pacientes refirieron **cefalea** <u>leve</u> (S1130-0108200400040004) Annotate only *cefalea* (C0018681 Headache, ICD-10: R51)

(136.) cifras consideradas **dolor** <u>moderado</u> (S0325-00752008000500004) Annotate only *dolor* (C0030193 Pain, ICD-10: R52)

(137.) presentaban obstrucción bronquial leve o moderada

Annotate only *obstrucción bronquial* (C0221725 Bronchial Obstruction)

Likewise, we do not annotate in the current version classifications of physical or functional state of pathologies, neoplasia stages, or values of the assessment of the oncologic quality of life; the UMLS tends to classify them as Findings:

(138.) pacientes con **falla cardiaca** <u>estado funcional II-IV</u> por más de 6 meses (S0120-56332018000200106) Annotate only *falla cardiaca* as DISO.

(139.) <u>clase funcional ii a iv</u> de la New York Heart Association (NYHA) (S0211-699519300529)

Do not annotate clase funcional ii a iv de la New York Heart Association (NYHA)

- (140.) **toxicidad gastrointestinal** aguda <u>Grado 1-2</u> (S0185-106317300264) Annotate only *toxicidad gastrointestinal* (C1142499 Gastrointestinal toxicity)
- (141.) con edades entre 20-65 años, 50-100 kg, estado físico ASA I-II-III

 Do not annotate estado físico ASA I-II-III (S0034-70942014000300177)
- (142.) Pacientes con **CVMI**, en estadio clínico <u>T2-T4a, N0, M0</u> (2017-004692-31) Annotate only CVMI ('Carcinoma de vejiga músculo invasivo')
- (143.) ECOG (Eastern Cooperative Oncology Group) 0-1 (2015-004816-39) Do not annotate anything.

(144.) 24 pacientes con **cirrosis alcohólica** (8 en <u>estadio B de Child-Pugh</u> y 16 en <u>estadio C Child-Pugh</u>) (S1130-01082008000800007)
Annotate only *cirrosis alcohólica* (C0023891 Liver Cirrhosis, Alcoholic, ICD-10: K70.30)

Besides, the UMLS includes the *Findings* category in the DISO semantic group. Despite their clinical relevance, most of these entity types were excluded in the current version of the corpus; e.q.:

- Findings referring to aspects addressed in the anamnesis: e.g. *divorciado*, C0086170; *alto*, C0241240...
- Findings expressing neuter information (not necessarily a pathologic condition): e.g. el 25% de los pacientes se hizo normoalbuminúrico (do not annotate normoalbuminúrico) (S0211-69952012000200010)
- Too general or vague terms, when they occur isolated: anomalía, hallazgo, problema...
- Terms such as historia de, antecedentes de...: e.g. antecedentes de drogadicción (annotate only drogadicción; S1134-80462013000600002)
- Variations in values of a measurement or lab test that are beyond upper or lower limits of normal: e.g. aumento de la fosfatasa alcalina (0211-699503016284; do not annotate aumento de la fosfatasa alcalina), descenso de colesterol LDL (0211-699505017919X), reducción de la presión arterial (S0211-69952012000800013), disminución de hemoglobina, etc.

- Abnormal results in laboratory analysis or examinations: e.g. bazo no palpable, examen neurológico anormal, anomalías de laboratorio...
- Findings of improvement or worsening patterns: <u>progresión</u> <u>del dolor torácico</u> (S0375-090615000543; annotate only <u>dolor torácico</u> as DISO). Two exceptions may appear:
 - 1) progresivo (adjetive) is annotated together with a term with an ICD-10 category: e.g. parálisis supranuclear progresiva (C0038868, ICD-10: G23.1)
 - progresión or progresivo is annotated with terms of oncologic processes, when it expresses the meaning of change in the disease or tumor stage: e.g. progresión del tumor (C0178874 Tumor Progression; Neoplastic Process)
- Findings related to life expectancy: e.g. muerte inminente, esperanza de vida inferior a un año...
- Findings related to medical devices: e.g. portador de marcapasos, portadores de prótesis valvulares...
- Findings related with nutritional or functional state, or lifestyle (sedentario, vegetariano...). However, we annotate tabaquismo, fumador or uso de drogas because there are ICD-10 categories (F17.200 and F19.20)
- Findings related with good or bad response to treatment, therapeutic failure... E.g. *fracaso del tratamiento*

We only annotate entities of type *Finding* if there is a category in the International Classification of Diseases vs 10 (ICD-10), but we generally exclude categories from the Z class referring to Histories, Factors or Social situations that affect the health state. We also annotate as DISO those entities that, in annotators' opinion, can be interpreted as signs or symptoms, pathologic functions, and/or are key to understand the text content.

```
    (145.) Treinta y cinco sujetos asintomáticos
        Annotate asintomáticos as DISO
    (146.) vómitos en "posos de café" (2016-003339-39)
        (C0278002 Vomit contains coffee grounds finding; ICD-10: K92.0)
    (147.) infiltrados radiológicos (2020-001445-39)
        (C0235896 Pulmonary Infiltrate, ICD-10: R91.8)
    (148.) embarazos múltiples (2013-003778-29)
        (C0032989 Multiple Pregnancy; ICD-10: O30.90)
```

Likewise, we also annotate as Findings the clinical signs revealing a pathologic state and observed in a diagnostic procedure or laboratory analysis; e.g.:

- Neurologic focality (abnormalities in a neurological exploration): e.g. signo de babinsky, signos meníngeos...
- Abdominal guarding: e.g. peritonismo
- Heart murmurs (abnormalities in a cardiopulmonary auscultation)

(149.) La **kaliemia** no se modificó. (S0211-69952012000200010)

We interpretate that the measurement result (*potassium level*) did not change (*Finding*), rather than the change in the analysis method (*potassium measurement*)

(150.) Valorar los cambios en el <u>umbral del **dolor** a la presión</u>
(S1134-80462010000700004)
Annotate *umbral del dolor a la presión* (PROC) and *dolor* (DISO)

The following scheme can help to understand the UMLS classification:

PROC
PHYS
DISO

Diagnostic or laboratory procedure

[tomar, controlar... la] presión arterial

presión arterial

Pathology

hipertensión

Entities expressing a clinical attribute or organic function are ambiguous (tensión arterial, frecuencia cardiaca, frecuencia respiratoria, saturación de oxígeno, etc.). In contexts where these entities co-occur with a number or figure, or with terms such as medir, valorar, etc., we interpretate them as 'mesurement' of that attribute and annotate them as PROC:

(151.) midieron la **presión arterial promedio** (**PAP**) y la **frecuencia cardíaca** (**FC**) Annotate as PROC: *presión arterial promedio*, *PAP*, *frecuencia cardíaca*, *FC*

Contexts such as *serología positiva*, *prueba de IgG+*, etc. are classed as Laboratory or Test Result in the UMLS Metathesaurus (PHYS semantic group). Some cases are also classed as Findings. Owing to this ambiguity, we only annotate PROC in the term referring to the analytic test (we do not annotate +, *positivo* or *negativo*):

(152.) Sífilis **IgG+** (2020-001565-37) Annotate DISO en Sífilis y PROC en IgG (sin carácter +)

However, exceptions are terms such as *VIH*+ or *VIH positivo*, which have an ICD-10 category (C4759637 HIV positive status) and are anotated as DISO:

(153.) Tratamiento antiviral o **VIH+** (2020-001565-37) Annotate DISO in *VIH*+ (also, *tratamiento antiviral* is annotated as PROC)

In this stage of the project, we do not annotate text fragments requiring medical knowledge to infer a pathological state:

(154.) peso al nacer menor o mayor de 800 g (...) **prematuros** con peso al nacimiento entre 500 y 1.250 g (S0370-41062014000300006) Only annotate *prematuros*.

(155.) Quince pacientes con (...) **frecuencia cardíaca** > 65 lpm Annotate *frecuencia cardíaca* as PROC. The text span expressing the measurement value (*frecuencia cardíaca* > 65 lpm) is **not** annotated as DISO because it requires inferring medical knowledge.

We recommend checking the UMLS Metathesaurus when hesitating about whether to annotate a Finding or not. **Do not annotate anything if the context is unclear**. Do not annotate either coordinate or juxtaposed structures where Findings are separated by several words expressing measurements or laboratory values (increased or reduced):

```
(156.) la fosforemia (5.9 \pm 0.6 \text{ a} 5.0 \pm 1.4 \text{ mg/dL}, p = 0.049), el producto calciofósforo (59.8 \pm 5.8 \text{ a} 48.6 \pm 12.5 \text{ mg2/dL2}, p = 0.01) y el colesterol (191 \pm 29 a 167 \pm 33 mg/dL, p = 0.02) <u>disminuyeron</u>. (0211-699503016284) Annotate fosforemia, producto calciofósforo and colesterol as PROC.
```

With regard to mutations, in the current version we only annotate the term *mutación* (C1705285 Mutation Abnormality; Cell or Molecular Dysfunction) or *deleción* (C1511760 Deletion Mutation; Cell or Molecular Dysfunction), or the mutation subtype (e.g. *mutación molecular*). The gen or exon involved is annotated GENE:

(157.) mutaciones de resistencia mayores a cualquiera de los fármacos Annotate mutaciones de resistencia (DISO) and fármacos (CHEM) (2016-005226-11)

(158.) **liposarcoma mixoide** con **mutación** PIK3CA (2013-005155-32) Annotate DISO in *liposarcoma mixoide* and in *mutación*; and annotate *PIK3CA* as GENE

(159.) **deleción** del exón 19 o **mutación** L858R en el exón 21 (2014-002565-30) Annotate DISO in *deleción* and in *mutación*.

GENE

Entities referring to genes and genetic material.

(160.) **mutación** en uno de los cinco <u>genes</u> <u>HMR (ASXL1, EZH2, SRSF2</u> e <u>IDH1/2</u>) (2014-004928-21) Annotate *mutación* (DISO) and *genes, ASXL1, EZH2, SRSF2, IDH1/2* (each with a different GENE entity)

LIVB

We have annotated the most adequate entities for the task, namely following:

Microorganisms or pathogens: viruses, fungi or bacteria (including probiotics).
 In contexts of metonymy (where the mention of a virus refers to the disease: e.g. virus de la hepatitis B, virus de inmunodeficiencia humana) we annotate
 DISO, if it can be interpretated as patological state (e.g. VIH+):

(161.) **Enfermedad hepática** de etiología diferente al **VHC** Annotate DISO in *enfermedad hepática* and *VHC* ('virus de la hepatis C') (S1025-028X2011000300001)

(162.) pacientes con **VIH/SIDA** naïve (S0716-10182019000100032)

In contexts such as *infección por VIH* or *infección VHC*, annotate DISO in the full entity and LIVB (as a nested entity) for the name of the virus or bacteria:

(163.) **pacientes** con **infección por VIH**/**SIDA**Annotate DISO in *infección por* VIH y SIDA; and LIVB in *pacientes* y VIH

 Population groups: we annotate entities referring to the participants in the clinical trial: paciente, hombres, mujeres...

(164.) **Varones** y **mujeres** con **18 años** de edad (2013-003645-42) Annotate LIVB in *varones*, *mujeres*, and Age in *18 años*

Entities referring to **patient groups** (i.e. suffering from a **pathology**: e.g. *diabético, infértil*) are annotated as **DISO**; likewise, patient groups experiencing a **physiological process** (e.g. *embarazadas*) are marked **PHYS**:

(165.) seis **diabéticos** consumieron dos **fórmulas** (S0212-16112017000300532) Annotate DISO In *diabéticos*, and CHEM in *fórmulas*

(166.) **anemia ferropénica** en la **embarazada** (S0212-16112017000300532) Annotate DISO in *anemia ferropénica*, and PHYS in *embarazadas*

If possible, annotate PHYS entities inside LIVB entities:

(167.) **embolia pulmonar** en las **mujeres <u>embarazadas</u>** (2012-001505-24) Annotate DISO in *embolia pulmonar;* LIVB in *mujeres embarazadas* (Pregnant Women, C0033011) and PHYS in *embarazadas*

 Age group: adolescente, sietemesino, adulto, anciano... These entities also express age and are also marked with the Age attribute:

LIVB [Age]

(168.) fibra en adultos

(169.) **niños** y **adolescentes** de **7 a 18 años** de edad (2008-005356-25) Annotate LIVB with Age attribute in *niños*, *adolescentes*; and annotate Age in *7 a 18 años*

• Entities expressing participants' demographic data: género femenino, género masculino, caucásico... The entity with the wider scope will be marked:

(192.) **participantes masculinos y femeninos** (2018-003711-21) Annotate LIVB in the full entity (do not annotate only *participantes*)

(193.) **Género femenino** (2013-000577-77) Annotate LIVB (C0043210 Woman).

(193.) de ambos sexos, edad entre 18 y 65 años, de origen caucásico (2013-001315-71)

Annotate LIVB in ambos sexos and caucásico, and Age in entre 18 y 65 años

Do not annotate a LIVB entity in very specific intervention groups (containing the name of the drug or procedure: e.g. *grupo lidocaína*), except in generalizable expression with a CUI (e.g. *grupo intervención*: C2986530 Intervention Group; *grupo control*, C0009932 Control Groups, *grupo experimental*, C5205743 Experimental Group):

(193.) 53 **pacientes** en el grupo de **Cefazolina** (S1022-51292011000400003) Annotate *pacientes* (LIVB) and *Cefazolina* (CHEM) (not *grupo de Cefazolina*)

(192.) el **grupo de <u>tratamiento</u>** recibió **40 mg** de **telmisartán** Annotate *grupo de tratamiento* (LIVB), *tratamiento* (PROC), *40 mg* (Dose) and *telmisartán* (CHEM)

PHYS

We annotate entities of the following UMLS semantic types:

- Biologic Function: e.g., *ingestión*
- Cell Function: e.g., meiosis
- Genetic Function: e.g., herencia autosómica
- Molecular Function: e.g., glucólisis
- Organ or Tissue Function: e.g., lagrimeo, tacto
- Organism Function: e.g., recuperación, sueño
- Physiologic Function: e.g., *menopausia*, *puerperio*

(170.) no se habían realizado **pruebas** en este **embarazo** (S1020-49892016001200455) Annotate *pruebas* (PROC) and *embarazo* (PHYS)

(171.) Pacientes en periodo de **menstruación** (2016-000371-24) Annotate *menstruación* as PHYS

We also annotate PHYS in expressions such as *efecto antiinflamatorio* (C1516019, Physiologic Function) or *efecto adrenérgico* (C3179174):

(172.) La ingesta de omega-3 se ha asociado con **efectos antinflamatorios** Annotate *efectos antinflamatorios* as PHYS (S0212-16112014001200013)

We also annotate PHYS in modifiers, adjetives or participle forms expressing pacient groups: e.g. *embarazadas*: *están embarazadas*, *quedarse embarazadas*...:

(173.) **embolia pulmonar** en las **mujeres embarazadas** (2012-001505-24) Annotate DISO in *embolia pulmonar;* LIVB in *mujeres embarazadas* (Pregnant Women, C0033011) and PHYS in *embarazadas*

We did not mark the following semantic types: *Organism Attribute* and *Clinical Attribute*: e.g. *postura* ('Body position', C1262869), sexo ('Sex', C1522384)...

We do not mark PHYS in names of institutions, medical departments or organisms:

(174.) Instituto del Sueño (S0066-782X2011000400006)

PROC

We include here entities from the following UMLS semantic types:

- Diagnostic Procedure: e.g. colonoscopia
- Health Care Activity: e.g. examen clínico
- Laboratory Procedure: e.g. hemograma
- Molecular Biology Research Technique: e.g. secuenciación del ADN
- Research Activity: e.g. farmacovigilancia. This category mainly includes entities expressing medical research tasks. Statistical analysis (e.g. t de student, ANOVA, regresión múltiple, coeficiente de correlación, etc.) are classified as concept entities (CONC) in the UMLS; therefore, we do not annotate them as PROC. Consequenty, we do not annotate as PROC other semantically-similar terms, even though they can be classed as PROC in UMLS: e.g. análisis estadístico (C0871424).
- Therapeutic or Preventive Procedure: e.g. diálisis de riñón

Examples:

```
(175.) mujeres hospitalizadas (S0104-11692016000100416)
```

(176.) complicaciones en el **cateterismo venoso** (S0104-11692016000100435)

Entities expressing measurements of chemical substantes or laboratory analyses (PROC) may include a CHEM entity. We annotate both the outer and inner entities:

```
(177.) Los niveles de PTH < 120 pg/ml en pacientes en diálisis
Annotate niveles de PTH (PROC) and PTH (CHEM) (0211-699500012506)
```

In general, the term *placebo* is annotated as PROC:

(178.) al grupo B se le indicó un placebo

(S0104-11692016000100434)

General words such as *técnica*, *aplicación*, *uso...* are only annotated when they are modified with an adjective or noun phrase specifying or describing the type of procedure; otherwise, do not annotate them (annotate only the more specific terms):

(179.) utilizando la misma **técnica quirúrgica** (S0009-741115001620) Annotate *técnica quirúrgica* as PROC.

(180.) Su uso en pacientes con **sedación profunda** es seguro y la <u>técnica</u> no se ve modificada (S1729-519X2016000500004)

Annotate *sedación profunda* as PROC, but not *técnica*.

With regard to chemotherapy regimens combining several drugs, each pharmacological substance is annotated separately (CHEM), even though the UMLS Metathesaurus often includes a CUI for the compound term:

(181.) **Nivolumab** más **Ipilimumab** en sujetos con **melanoma** (2016-001941-26) Annotate as CHEM *nivolumab* and *ipilimumab*, and *melanoma* as DISO.

General verbs expressing analysis, study or data evaluation are not annotated as PROC when they occur without object or complement: e.g. analizar, comparar, estudia, evaluar, valorar... We only annotate these verbs with the object specifying the type of procedure or analysis (e.g. valorar la eficacia y seguridad).

(182.) Analizar la eficacia y la seguridad de la trombólisis intraarterial (\$0210-56912010000600003)

Annotate Analizar la eficacia y la seguridad (PROC) and trombólisis intraarterial (DISO)

Entities such as *ensayo*, *estudio*, *análisis*, *investigación*, etc. are not annotated in isolation; we annotate them in compound terms detailing the type of trial, analysis or study (see more details below):

(183.) Análisis sanguíneos que indiquen función hepática anormal

(2019-002626-67)

Annotate análisis sanguíneos (PROC) and función hepática anormal (DISO).

(184.) Sin contraindicación mayor a ninguno de los **fármacos** en estudio Do not annotate *estudio.* (2019-002626-67)

Only annotate *análisis* or *ensayo* without any complement in contexts where they refer to 'laboratory analysis' or 'immunoassay':

(185.) El **ensayo** anti-CCP2 mostró un mejor balance sensibilidad (48,5%) y especificidad (98,0%) (S1729-519X2018000400540)

(186.) valor de paciente normal para el laboratorio que realiza el **análisis** (2016-002554-21)

Entities describing or specifying the type of clinical trial are fully annotated, including the phase of the trial, the use of control intervention or placebo, whether it is randomized or not, simple or double blind, unicentric or multicentric:

(187.) ensayo clínico aleatorizado y controlado (Fase-IIb) a doble ciego (S1729-519X2016000500004)

(188.) ensayo clínico controlado con placebo, aleatorizado y a doble ciego (\$1025-028X2011000300001)

However, we tend to avoid annotating temporal expressions or the number of participants; that is, we do not annotate specific data that may not generalize enough to other contexts:

(189.) **ensayo clínico prospectivo no aleatorio** <u>de dos grupos de pacientes</u>
Do not annotate *de dos grupos de pacientes.* (S1130-01082005000500005)

(190.) Estudio prospectivo de intervención no controlado ni aleatorizado de tres años de seguimiento (S2011-69952012000200010)

Do not annotate de tres años de seguimiento.

Likewise, we do not annotate in the entity expressing the type of trial other entities referring to the intervention therapy or the pathology considered:

(191.) Estudio de evaluación de la seguridad y la eficacia en pacientes de pegunigalsidasa alfa (PRX-102) con la enfermedad de Fabry (2018-001148-67) Annotate as PROC: Estudio de evaluación de la seguridad y la eficacia Also, annotate (out of the PROC entity): pegunigalsidasa alfa (CHEM), PRX-102 (CHEM) and enfermedad de Fabry (DISO).

To avoid long annotations, we tend to annotate in one PROC entity the type of trial or study, and we annotate the goal or objective in a different PROC entity:

(192.) [Estudio multicéntrico, aleatorizado, doble ciego, con control activo] para [evaluar la eficacia] en la semana 52 de secukinumab (2015-004477-32) Annotate 2 PROC entities: Estudio multicéntrico, aleatorizado, doble ciego, con control activo, y evaluar la eficacia; also, annotate secukinumab (CHEM)

The following is a non-exhaustive list of the types of analyses or studies we annotate:

- Efficacy analysis, safety and tolerability studies
- Pharmacokinetic and/or pharmacodynamic studies
- Survival analysis and/or follow-up studies
- Cost-effectiveness analyses
- Intention-to-treat analyses (C2718028)
- Descriptive studies, comparative, prospective or retrospective analyses
- Observational and/or exploratory studies, intervention studies, and pilot studies
- Extension trials and open-label studies (C1709323)

 Comparative and non-comparative studies (two or more cohort groups, nested clinical trials...)

MEDICATION INFORMATION

Mode or administration route (Route)

We mark as Route those entities expressing modes o administration routes of drugs, substances or foof (note that the UMLS classifies these entities as CONC):

(193.) recibieron 5 mg orales de ácido fólico (0211-699501013259)

(194.) infusión de dexmedetomidina intravenosa (S1134-80462015000100002)

(195.) nutrición <u>parenteral</u> (S0370-41062014000300006) Annotate PROC in *nutrición parenteral*, and Route in *parenteral*

Note that *oral* is annotated as ANAT in the following context:

(196.) acumulación de bacterias en la cavidad **oral** (S0716-10182013000400003)

Inside PROC entities, Route is marked if it expresses the drug administration route:

(197.) infusiones intraperitoneales de anestésicos locales

(S0034-70942007000400002)

Annotate *infusiones intraperitoneales* as PROC (C0031146 intraperitoneal infusion), *intraperitoneales* (Route) and *anestésicos locales* as CHEM (C0002934; Local Anesthetics; Organic Chemical; Pharmacologic Substance).

If an entity can be labeled as a procedure (PROC) or the administration route (Route), we annotate PROC:

(198.) recibieron una **infusión** de **ocitocina** (S0034-70942012000500003) Annotate *infusión* as PROC and *ocitocina* as CHEM

Note that we do not annotate ANAT nor Route in words expressing the surgical approach of a procedure:

(199.) Cirugía transnasal transesfenoidal endoscópica

(S1130-14732005000100004)

Annotate *cirugía transnasal transesfenoidal endoscópica* as PROC; do not annotate *transnasal* nor *transesfenoidal* (surgical approach)

(200.) la realización de biopsia prostática transrectal ecodirigida

(S0004-06142009000500003)

Annotate biopsia prostática transrectal ecodirigida (PROC) and prostática (ANAT); do not annotate transrectal (surgical approach)

Annotate CHEM in the drug or pharmacological substance, and Route in the entity expressing administration mode or route:

(201.) **pantoprazol** por <u>vía intravenosa</u> (S1130-01082008000800004) Annotate *pantoprazol* as CHEM and *vía intravenosa* as Route

(202.) el consumo de **anestésicos <u>venosos</u>** (S0034-70942004000100013) Annotate *anestésicos* as CHEM y *venosos* as Route

(203.) **citrato de fentanilo <u>oral transmucoso</u>** (S1134-80462010000300002) Annotate CHEM in *citrato de fentanilo oral transmucoso* (C3853047; Transmucosal Oral Fentanyl Citrate, Organic Chemical) and *oral transmucoso* as Route

Dose, concentration or strength

Entities indicating the quantity of the drug supplied (e.g. in milligrams, percentage...):

(204.) **tintura de propóleos <u>al 10%</u>** (S0034-75072007000300006) Annotate *tintura de propóleos* as CHEM and *al 10%* como Dose.

(205.) **calcio** en dosis de <u>1.000 mg</u> **cada 24 horas** (S0212-16112015000500025)

Annotate calcio as CHEM; 1000 mg as Dose; and cada 24 horas as Frequency.

Annotate also the number of medication intakes:

(206.) dosis recomendadas de **5 frascos** (S0121-07932007000300002)

(207.) <u>múltiples dosis</u> de insulina (2015-002963-40) Annotate as Dose: *múltiples dosis*; and *insulina* (CHEM)

(208.) <u>3 inyecciones</u> preprandiales de análogo de insulina rápida (2015-002963-40)

Annotate as Dose: 3 inyecciones; annotate also preprandiales (Time), inyecciones (PROC) and análogo de insulina rápida (CHEM)

Dose expressions in ranges, enumerations or coordinated phrases are marked in one entity:

(209.) **1, 2-4 o más de 4 <u>comprimidos</u>** al día (S1130-63432014000400005) Annotate as Dose the full entity (*1, 2-4 o más de 4 comprimidos*); annotate also *comprimidos* (Form) and *al día* (Frequency)

(210.) <u>1-2 inyecciones</u> diarias de insulina Detemir (2015-002963-40) Annotate as Dose the full entity (*1-2 inyecciones*); annotate also *inyecciones* (PROC), *diarias* (Frequency) and *insulina Detemir* (CHEM)

(211.) **AT** por **vía oral** a razón de **50-100 mg** (S0025-76802004000100001)

Annotate one Dose entity (50-100 mg); annotate also *vía oral* (Route) and AT (CHEM)

Some unspecified dose entities are also annotated:

(212.) quimioterapia en **dosis altas** (2017-002238-21) Annotate *dosis altas* as Dose

(213.) **anticoagulantes** a **dosis terapéuticas** (2013-000619-26) Annotate *dosis terapéuticas* as Dose and *anticoagulantes* as CHEM

However, expressions of dose variation (increase or decrease) are annotated PROC (they are interpreted as a therapeutic intervention):

(214.) Dexametasona (**4mg** cada 8h, re-evaluación a las 72h y **disminución progresiva de dosis**) (S1130-14732009000400003) Annotate *4mg* as Dose and *disminución progresiva de dosis* as PROC (C1827449 Drug Tapering; Therapeutic or Preventive Procedure)

(215.) permite **disminución la dosis** de morfina Annotate *disminución de dosis* as PROC (C2348004 Agent Dose Decreased)

(216.) **aumentos de dosis** de **remifentanilo** (S0034-70942014000200073) Annotate *aumentos de dosis* (C1707810 Dose Increased, PROC).

Drug dosage form

Annotate entities such as: aerosol, cápsulas, comprimidos, crema, formulación, gel, gotas, tabletas...

(217.) comparar la efectividad de **800 Ul/día** de **D2** (<u>gotas</u>) y **D3** (<u>comprimidos</u>) (S0025-76802012000300002)

Annotate *D2* (C0014695 Ergocalciferol) and D3 (C0008318 Cholecalciferol) as CHEM; *gotas, comprimidos* as Form; *800 UI/día* (Dose), *800 UI* (Dose); and */día* (Frequency).

(218.) **12,5 gr** de <u>gel</u> con **250 mgr** de hidrocloruro de lidocaína intra-rectal (\$0004-06142009000500003)

Annotate hidrocloruro de lidocaína as CHEM; gel as Form; 12,5 gr and 250 mgr as Dose; and intra-rectal as Route.

(219.) montelukast en tabletas masticables de 5 mg

(S0120-41572012000300010)

Annotate *montelukast* as CHEM; *tabletas masticables* as Form; and *5 mg* as Dose.

The word *solución* ('solution') is annotated CHEM in compound entities indicating the drug substance (e.g. *solución glucosada*), or if we can interprete that *solución* implies a solution containing a diluted drug:

(220.) uso de la **solución glucosada** por **vía oral** (S0325-00752008000500004) Annotate *solución glucosada* as CHEM, and *vía oral* as Route.

(221.) Las soluciones hipotónicas se han vinculado a la producción de hiponatremia iatrogénica (S0325-00752013000400005) Annotate CHEM in soluciones hipotónicas (C0020677 Hypotonic Solutions) and DISO in hiponatremia iatrogénica

TEMPORAL ENTITIES

We followed the TimeML³ standard (TIMEX3 version) to annotate time expressions (*TIMEX*). Nevertheless, there are some differences with regard to the scheme of the THYME corpus (Styler et al. 2014):

- 1) Entity subtypes are annotated as classes and not as attributes of a general temporal expression class.
- 2) Entities of type Quantifier are not annotated.
- 3) Entities of type *Prepostexp* (with prefix *pre/post-*: e.g. *preoperative*, *postprandial*) are annotated as Date or part of the day (Time).
- 4) Entities expressing age are annotated (Age).
- 5) Except for dates, coordinated expressions are annotated in the same entity: e.g.
- 3. 6 and 12 months (annotate one Duration entity).

In summary, we have followed the TimeML standard, but adapted it to our task. For all classes:

1) Only annotate entities with words expressing temporal information (*día, año, mes, minuto,* or numbers of dates: e.g. 2005). Do not annotate patologies or procedures (DISO or PROC) inside a temporal entity. In the TimeML schema, those are considered EVENTS and are linked using temporal relations (TLINK):

(222.) se registró el total de movimientos **al primer minuto** después de la **intubación** (S0034-70942014000600425)

Annotate al primer minuto but not después de la intubación (only intubación is annotated as PROC)

(223.) 5min después de la intervención y 24horas después de la intervención (S1134-80462010000700004)

Annotate two Duration entities: *5min* and *24 horas* (*intervención* is PROC)

2) Do not annotate prepositions or adverbs introducing the temporal expression, except in case of ambiguitity (e.g. *mañana*, 'tomorrow' vs. *por la mañana*, 'in the morning'):

(224.) En **1994** se publicaron los resultados (\$0370-41062001000100013) Annotate *1994* (no *en*)

(225.) comunicación diaria por teléfono hasta el 3º día

³ https://www.cs.brandeis.edu/~cs112/cs112-2004/annPS/TimeML12wp.htm

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Annotate *el 3º día*, without *hasta* (Date) and *diaria* (Frequency) (S0034-70942010000200002)

3) Segmentation errors are also annotated:

(226.) **5min** después de la intervención Annotate *5min*

4) Expressions with ellipsis of temporal words are only annotated if some information to understand the text would be lost if not annotated:

(227.) la frecuencia de sesiones con las que el paciente inicia HD (una o 2 sesiones por semana) es menor que en la HD convencional (3 por semana). Dicha frecuencia aumenta (de una a 2, y de 2 a 3) (S0211-699518301425) Annotate Frequency only in una o 2 sesiones por semana and in 3 por semana

(228.) dexametasona **la primera semana** y fluorometalona **las tres siguientes** (S0365-66912005000100004)

Annotate *la primera semana* y *las tres siguientes* (otherwise, information is lost)

Age

Age is annotated both in years and months (for child population). Note that the word edad is not annotated:

(229.) Diez varones, con una edad media de **59 años** (S0210-56912010000600003)

(230.) pacientes pediátricos de **12 meses** de edad (S0120-41572012000300010)

When age is expressed in ranges, only one entity is marked:

(231.) Hombres y mujeres de **18-75 años** de edad (2013-003588-73) Annotate one Age entity

Modifiers (mayor/menor de) or characters such ≥ as are also annotated:

(232.) mujeres **mayores de 25 años** (S0185-106317300069)

(233.) Edad : **≥18 años y < 90 años** (2020-001541-39) Annotate one Age entity

Translation errors are not marked; e.g. do not annotate \geq 18 years.

Entities expressing age groups (e.g. *adolescente, joven, sietemesino, mayor de edad...*) are annotated LIVB with the Age attribute:

(234.) **adolescentes** (edades de **12 a 18 años**) (2015-003314-24) One Age entity (*12 a 18 años*) and *adolescentes* as LIVB (with *Age* attribute).

Date

This class gathers entities expressing dates or indefinite temporal location longer than one da. It is not necessary to include the introductory adverb or preposition in these expressions:

```
(235.) En 1994 se publicaron los resultados (S0370-41062001000100013) Annotate 1994 (without en)

(236.) Analizados desde el 1/1/1995 (S0370-41062001000100013) Annotate 1/1/1995 (without desde)

(237.) desde el tercer mes (0211-699505018925) Annotate el tercer mes (without desde)
```

In entities with *hace* + temporal expression ('ago'), *hace* is included in the full expression (so that it is not interpreted as duration):

```
(238.) FA hace menos de un año (S0066-782X2010001600013) Annotate hace menos de un año (Date) and FA (DISO)
```

Do not annotate vague expressions such as al inicio, al final, inicialmente, al principio...

```
(239.) <u>Al final</u> de cada intervención no se observaron cambios
No anotar ninguna entidad temporal. (S0212-16112014001200013)
```

Only annotate vague expressions such as the following ones:

```
(240.) fecha límite aproximada, finales de marzo de 2013 (2013-003866-15) (241.) un 50% presenta actualmente valores negativos (S0212-71992005001000008)
```

In the following cases, according to the TimeML criteria, two entities are marked, rather than one:

```
Annotate two Date entities: Octubre 2001 and Junio 2003.

(243.) durante el periodo 2001-2003 (S0036-36342004000400008)

Annotate two Date entities Date: 2001 and 2003.
```

(242.) entre Octubre 2001 y Junio 2013 (S2306-41022014000400005)

(244.) entre **enero** y **diciembre de 2012** (S1561-31942015000400005) Annotate two Date entities.

(245.) estableciendo los controles al día siguiente, a la semana, al mes y a los 3 meses de la cirugía (\$0365-66912010000800003)

Annotate 4 Date entities: al día siguiente, a la semana, al mes, a los 3 meses

Pre-/post- expressions are generally underspecified and it is not always possible to link them to a date or time frame. These cases will be interpreted according to the context:

(246.) **náuseas y vómito** en el **postoperatorio** (S0034-70942015000300191) Annotate *postoperatorio* as Time; and *náuseas y vómito* as DISO

(247.) **pravastatina preoperatoria** (S0185-106317300069) Annotate *pravastatina* (CHEM) and *preoperatoria* as Time

Duration

This class is used for entities expressing how long the event lasts.

(248.) tras un seguimiento de **dos años** (S1698-69462006000200015) Annotate 2 *años*

The preposition or adverb introducing the expression is not marked: e.g. annotate 2 horas (not durante dos horas).

(249.) se dio seguimiento a 88 pacientes durante **4 años**Annotate *4 años* as Duration (S0212-16112016000200036)

(250.) Cefazolina 1 g tid EV. x **7 dias** (S1022-51292011000400003) Annotate *7 dias* as Duration

Duration is also marked in entities expressing a time interval:

(251.) Se analizaron los datos a los **6 meses** (S0211-699519300529) Annotate *6 meses* as Duration

(252.) estado vital a **40 semanas** (S0124-0064_PMID23250319) Annotate *40 semanas* as Duration

Note that we annotate together in one entity coordinated duration expressions (given that we do not normalize time expressions to time points in our task):

(253.) el seguimiento se realizó a los **12 y 24 meses**Annotate one Duration entity (S1137-66272013000300007)

We do not annotate adjetives such as *antiguo*, *moderno*... Only adjetives such as *anterior*, *posterior*, *siguiente*, etc. are marked in relative time expressions:

(254.) en **los siguientes doce meses**, el **clopidogrel** no se administraba (S0210-56912007000400001)

Annotate los siguientes doce meses (Duration) and clopidogrel (CHEM)

We also annotate indefinite modifiers or quantifiers such as y más, al menos...:

(255.) AZT vía oral durante **un mes o más**Annotate *un mes o más* as Duration

(256.) **al menos dos días** con pirosis
Annotate *al menos dos días* as Duration

(S0370-41062001000100013)

(S1130-01082006000300003)

In contexts of ambiguity, Duration shall be noted, especially when the period or time interval cannot be associated with a chronological date, or is associated to a drug or treatment.

(257.) Después de **dos meses** se midieron los niveles de hemoglobina Annotate *dos meses* as Duration (S0120-41572013000300003)

(258.) han iniciado recientemente la anticoagulación oral (**menos de 1 mes** antes de la selección) (2018-000753-45) Annotate *menos de 1 mes* as Duration.

(259.) Uso de un fármaco en investigación en los 30 días previos a la visita (set67/2017-000250-19)

Annotate 30 días as Duration and fármaco (CHEM)

(260.) después de **6 horas** de **bloqueo** (S0034-70942010000200004) Annotate *6 horas* (Duration) and *bloqueo* (PROC).

Frequency

Entities that express how often the event occurs, including the frequency of taking or administering a drug. In some annotation standards, this is called Set.

```
(261.) Las medidas se realizaron cada dos minutos (S0365-66912009000100004)
```

(262.) Los efectos adversos se dieron a menudo (S0034-70942010000200003)

(263.) placebo (n = 43) 1 vez/día (S0212-16112016000400031)

(264.) **800 UI<u>/día</u>** (S0025-76802012000300002)

Annotate 800 UI (Dose); and /día (Frequency).

(265.) Raltegravir (**1200 mg QD**) (2017-000986-60) Annotate Frequency in *QD* ('quaque die', 'una vez al día') and *1200 mg* (Dose)

Abbreviations of frequency expressions not related to the intake of a pharmacological substance or the administration of a therapeutic procedure are not annotated (we do not consider them necessary for the task).

(266.) el filtrado glomerular estimado se redujo (69,8 \pm 29,7 vs. 60,25 \pm 23,0 ml/min/m2) (S0211-69952012000200010) No es necesario anotar /min

(267.) flujo arterial medio 354,16 ml/min (S0211-69952010000300018) No es necesario anotar /min

(268.) El grupo I (infusión) recibió 0,5 mg/kg/min de esmolol

(S0034-70942014000400247)

Note that we do annotate /min (Frequency) in this context because it refers to the infusion frequency (PROC) of esmolol (CHEM), with a dose of 0,5 mg/kg (Dose)

(269.) recibió **lidocaína 1.5 mg/kg/h** (S2448-87712017000200009) Note that we do annotate /h (Frequency) because it refers to the frecuency of lidocaíne administration (*lidocaína*, CHEM) with a dose of 1.5 mg/kg (Dose)

Time

Entities expressing hours or parts of the day.

(270.) un ayuno **nocturno** de **12 horas** (S0034-75072007000400001) Annotate *nocturno* (Time) and *12 horas* (Duration)

(271.) **10** g por la mañana

(S0212-16112011000100009)

Annotate 10 g (Dose) and por la mañana (Time). Do not annotate mañana as an isolate expression because it is ambiguous with other temporal expressions.

Temporal entities with prefix *intra-*, and expressions such as *preprandial* or *postprandial*, are interpreted as Time:

(272.) El uso de **opiáceos** en el **período intraoperatorio** (S0034-70942015000300191) Annotate *período intraoperatorio* as Time, and *opiáceos* as CHEM

(273.) un pico de **glicemia postprandial** (S0212-16112014000300013) Annotate *glicemia postprandial* (PROC) and *postprandial* (Time)

However, according to TimeML, Duration is marked in cases where time is measured in hours (e.g. *2 horas*, *24 horas*) and if expressions cannot be associated with a part of the day or a chronological time:

(274.) evaluación a **las 4 horas** del **postoperatorio** (S0120-33472007000400003) Annotate *las 4 horas* (Duration) and *postoperatorio* (Time)

(275.) El **torniquete** fue retirado después de **1 min** (S0034-70942014000300169) Annotate *1 min* (Duration) and *torniquete* (DEVI)

(276.) a las 2, 6 y 24 horas (S1134-80462015000500003) Annotate one Duration entity (277.) El hematocrito <u>posoperatorio</u> a las **24, 48 y 72 h** Anotar one Duration entity; annotate also *posoperatorio* (TIME) (S1134-80462015000500003)

2. CRITERIA FOR AMBIGUITIES

Chemical entities (CHEM) and Laboratory analysis (PROC)

Some entities might be annotated both as chemical substances (CHEM) and laboratory analysis or measurement of chemical substances (PROC). Although some contexts are often unclear, we mark only one semantic group to avoid noise when training the machine-learning algorithm. We tend to label CHEM in ambiguous contexts; the following are some criteria:

CHEM: annotate only chemical entity when the context does not convey any
meaning related to laboratory results, measurements of substances or
procedures; in general, contexts referring to a pharmacological substance (the
interventional drug, the administered medication...):

```
(278.) reciben carbonato cálcico a dosis de 2.500 mg/día (CHEM) (0211-699500012698)
```

```
(279.) dosis de EPO (Ul/semana) mensual (0211-699500012698) Annotate EPO as CHEM.
```

PROC: we annotate as PROC entities that can be interpreted as analysis / measurement of + chemical substance. Frequently, these contexts report results or values of lab procedures, and include terms such as analítica or verbs such as se midió, se analizó, se cuantificó... The following are other noun phrases often interpretated as PROC: medición de + CHEM (e.g. medición de calcio) CHEM total (e.g. calcio total), valores de + CHEM, cifras de + CHEM...

```
(280.) En grupo I aumentaron PTH (basal: 38,75 \pm 41, final: 99 \pm 69, p < 0,01) y fosfatasa alcalina (0211-699500012506) Annotate PTH and fosfatasa alcalina as PROC (Laboratory Procedure).
```

```
(281.) analíticas: hemograma, albúmina y creatinina séricas (0211-699502014854)
```

Annotate hemograma, albúmina and creatinina séricas as PROC.

Terms such as *inyección* or *vacunación* are annotated as PROC when they are interpretated as the therapeutic procedure. The word *vacuna* is annotated as CHEM when it refers to the medical drug or the pharmacological substance:

```
(282.) la inyección de propofol (S1025-028X2011000300001)
Annotate inyección as PROC and propofol as CHEM.
```

(283.) existía relación causal con la vacunación

Annotate vacunación as PROC

(S1025-028X2005000100002)

(284.) la reactogenicidad de la **vacuna** es escasa Annotate *vacuna* as CHEM. (S1025-028X2005000100002)

Ambiguity between chemical entities (CHEM) and body substances (ANAT)

We annotate chemical or pharmacological entities (CHEM) on mentions referring to substances that are administered as interventions or therapeutic procedures:

```
(285.) Aplicación de sellante de fibrina (S0009-741115002261) Annotate aplicación (PROC) and sellante de fibrina (CHEM) (fibrina is not ANAT)
```

On the contrary, we interpretate as anatomical entity (ANAT) from molecular level the el rest of macromolecules, cell components or body substances.

```
(286.) efecto genotóxico en linfocitos humanos (S0716-10182014000500006) Annotate linfocitos humanos (ANAT) and efecto genotóxico (DISO)
```

We annotate the term *suero* as ANAT when we interpretate it as 'plasma', 'the liquid substance of the blood'; and we annotate it as CHEM when it has the meaning of 'therapeutic solution':

```
(287.) el <u>nivel de betatrofina en suero</u> fue más elevado (...) la betatrofina en suero desempeña una importante labor en síndrome metabólico (S0212-16112016000200019)

Annotate suero (ANAT); betatrofina (CHEM) and nivel de betatrofina en suero (PROC)
```

```
(288.) pacientes deshidratados por diarrea aguda, menores de cinco años, recibieron suero oral (S0036-36342002000100003) Annotate suero as CHEM
```

Entities such as *plasma rico en plaquetas, plasma rico en factores de crecimiento* or *concentrados de hematíes* are interpretated as CHEM owing to the pharmacological processing they require to be produced:

```
(289.) tratamiento guiado con ecografía mediante Plasma Rico en Plaquetas (2018-003709-25) (C2362067 Platelet concentrate; Amino Acid, Peptide, or Protein; Pharmacologic Substance)
```

Regarding cell receptors, the UMLS ontological scheme classifies them as CHEM, even though these entities could be considered as ANAT:

(290.) antagonistas del receptor AT1 de angiotensina II, al bloquear más el receptor AT1, debería producir mayores beneficios (S0211-69952012000200010) Annotate 2 CHEM entities: antagonistas del receptor AT1 de angiotensina II (C0521942, Angiotensin II receptor antagonist) and receptor AT1 (C0529330, Receptor, Angiotensin, Type 1)

(291.) **pantoprazol** por vía <u>intravenosa</u> (S1130-01082008000800004) Annotate only *pantoprazol* as CHEM

(292.) el consumo de **anestésicos** <u>venosos</u> (S0034-70942004000100013) Annotate only *anestésicos* as CHEM

(293.) **citrato de fentanilo <u>oral</u> transmucoso** (S1134-80462010000300002) Annotate as CHEM the full mention *citrato de fentanilo oral transmucoso* (C3853047; Transmucosal Oral Fentanyl Citrate, Organic Chemical)

Entities referring to diagnostic measurement scales

Only entities found in the UMLS and with PROC semantic type will be annotated (because they can be interpretated as diagnostic procedure; e.g. WAIS intelligence test, CUI C2609456):

(294.) valoración subjetiva del dolor mediante la **escala visual analógica (EVA)** (S2306-41022015000100005)

Annotate escala visual analógica and EVA (PROC, CUI C0042815)

(295.) evolución funcional por **escala de Rankin modificada** (S0210-56912010000600003)

Annotate escala de Rankin modificada (PROC in the UMLS, CUI: C3888574)

(296.) evaluación por Escala de Glasgow para un seguimiento Annotate PROC in evaluación por Escala de Glasgow (C0278349 Glasgow coma testing and evaluation) and PROC in seguimiento

We do not annotate terms classified as scale or classification in the UMLS, but not classified as diagnostic procedure (e.g. escala or puntaje):

(297.) presentaron menor escore de sedación según la <u>escala de Ramsay</u> (S0066-782X2011000300008)

Do not annotate *escala de Ramsay* (concept entity, CONC: C0559295 Ramsay sedation scale; Intellectual Product)

(298.) Impresión Clínica Global (S0211-57352011000100002) Do not annotate (C3639708 Clinical global impression scale, CONC)

(299.) Inventario de Discapacidad de Sheehan (S0211-57352011000100002) Do not annotate (C4720840 Sheehan disability scale, CONC)

Entities referring to Associations, Medical specialties or Hospital units

These types of entities (and the nested entities inside them) are not annotated:

(300.) en la <u>Unidad de Digestivo</u> del Complejo Hospitalario de Ciudad Real Do not annotate *Unidad de Digestivo* nor *Digestivo* (S0212-71992005001000008)

(301.) <u>American Diabetes Association</u> (S0211-69952012000200010) Do not annotate *American Diabetes Association* nor *Diabetes*.

1. APPENDIX

List of modifiers

The following list might help to decide the types of modifiers to be annotated together with a core medical term; in general, we annotate an entity with modifiers:

- When the full term can be mapped to an ICD-10 category (in the case of DISO entities) or to an UMLS CUI (in the case of PROC entities).
- When it is necessary to understand the context or the content of the trial.

To avoid fragmented annotations, we do not annotate modifiers in attributive or copulative constructions (with the verb *ser*):

(302.) El grado final de **envenenamiento** fue leve en 13 (24,5%), moderado en 30 (56,6%) y grave (S0121-07932007000300002)
Annotate only *envenenamiento* (DISO); do not label *grave*, *leve* or *moderado*.

Annotate Do not annotate

Specific temporal modifiers or adjectives in multi-word terms, when they can be mapped to a CUI or ICD-10 category:

crónico: e.g. *fisura anal crónica* (ICD-10: K60.1, C0349071 Chronic anal fissure)

postoperatorio: e.g. dolor postoperatorio (C0030201 postoperative pain; ICD-10: G89.18)

postpunción: e.g. cefalea post-punción lumbar (C2875393 Headache due to lumbar puncture; ICD-10: G97.1)

postprandial: e.g. glicemia postprandial (C4700958 postprandial glucose in serum or plasma)

Vague temporal qualifiers: actual, anterior, futuro, inicial, inmediato, precoz, previo, siguiente, posterior, reciente...

Exceptionally, we annotate these adjectives if they are necessary to understand the context, or if the adjective distinguishes different concepts (CUI exist):

E.g. *inflamación persistente* (C1265824 Persistent inflammation)

E.g. eyaculación precoz (C0033038, ICD-10: F52.4)

E.g. seguimiento a largo plazo (C1517942 Long-term Follow-up)

We do not annotate adjetives expressing frequency: diario, frecuente, periódico, semanal...

Adjectives describing spatial position or localization, preferently only when an ICD-10 category or an UMLS CUI exists, or if they are needed to understand the text content:

alta: e.g. en endoscopia alta (C0017195 upper endoscopy)

central: e.g. sistema nervioso central

Past participles without specific details or descriptive information about the term:

administrado asociado conocido empleado especializado establecido

(C1269563 central nervous system) generado realizado local: e.g. anestésico local (C0002934 reconocido Local Anesthetics) relacionado superior (e.g. miembro superior, sometido C1140618 Upper Extremity) tratado unilateral: e.g. dolor unilateral (C0747150 pain unilateral; Sign or Symptom) Vague qualifiers and adjetives not Relational adjetives, descriptors of specific properties or features, describing specific details: or modifiers expressing a subtype or class diferente of pathology, if an ICD-10 category or distinto **UMLS CUI exists:** diverso clínico: e.g. ensayo clínico (C0008976 mismo Clinical Trial) nuevo principal medible: ej, enfermedad medible solo (C1513041 Measurable Disease), único lesión no medible (C1334988 Non-Measurable Lesion) Adjetives describing the type procedure (the Comparator), or when they are needed to understand the context: convencional: e.g. cirugía convencional (C1521745 Conventional Surgery) estándar: e.g. tratamiento estándar (C4684780 Standard Treatment) refractario: we only annotate it with the refractario a + phrase: we do not core term when this adjective is not annotate it when other phrases modified by other phrases (to avoid long modify it (to avoid long annotations): annotations) or when the full term has an E.g. hipertensión intracraneal (HIC) **UMLS CUI:** refractaria a las medidas de primer E.g. dolor refractario nivel (C0030200 Refractory Pain) Annotate only hipertensión intracraneal secundario: we annotate it when it has secundario a: do not annotate it when the sense of 'caused by other factor' (e.g. other phrases or complements modify a pathology) in constructions without this adjective, except in contexts phrases, and when the full term can be where the full term helps

mapped to an ICD-10 category:

understand the text content:

E.g. *hiperparatiroidismo secundario* en diálisis

Annotate hiperatiroidismo secundario (C0494305 Secondary

hyperparathyroidism, ICD-10: E21.1)

E.g. rectorragia crónica <u>secundaria a</u> la proctopatía por radiación

Annotate two different terms: rectorragia and proctopatía por radiación

Adjectives expressing recurrence or relapse: we only annotate them when the full term has an ICD-10 category or an UMLS CUI; or when the annotation is needed to understand the text contents:

recidivante: e.g. pterigium recidivante (C0155158 Recurrent pterygium,

ICD-10: 11.06)

recurrente: e.g. estomatitis aftosa recurrente (C2937365 Recurrent aphthous stomatitis; ICD-10: K12.0)

remitente: e.g. esclerosis múltiple remitente-recurrente (C0751967 Multiple Sclerosis, Relapsing-Remitting)

Evaluative adjetives:

beneficioso bueno efectivo fundamental ideal incómodo malo útil viable

Descriptors of the manner in which a procedure is done or applied, or adjectives expressing the extension of a pathological process: we only annotate terms having a CUI, or when the full term is needed to understand the context:

activo: annotate only in terms with an UMLS CUI:

E.g. *Inmunización activa* (C0042196 Active immunization)

E.g. *EC fistulosa* <u>activa</u>
Annotate only *EC fistulosa* (C3509259 crohn's disease with fistula)

abierto: e.g. cirugía abierta (C4283938 Open Surgical Procedure)

basal: e.g. tasa metabólica basal (C0542499 Measurement of basal metabolic rate)

continuo: e.g. perfusión continua (C0444889 Continuous infusion)

descompensado: e.g. EPOC descompensado (C2887446

Decompensated COPD; ICD-10: J44.1)

Comparative adjetives:

inferior (que) mayor (que) mejor (que) peor (que) superior (que)

Except in contexts where the adjective needs to be annotated with the main term, because there is an ICD-10 category or UMLS CUI:

Cirugía mayor (C0679637 major surgery)

Trastorno depresivo mayor (C1269683 Major Depressive Disorder, ICD-10: F32.9) primario: e.g. hipertiroidismo primario, C0221002 Hyperparathyroidism, Primary; ICD-10: E21.0)

sistémico: e.g. esclerosis sistémica, (C0477589 systemic sclerosis, ICD-10: M34.8)

total: e.g. anestesia intravenosa total (C0473965, Total intravenous anesthesia)

Descriptors of severity or pathological stage: we only annotate them when a full term has an ICD-10 category:

grave: e.g. miastenia grave (C0026896 Myasthenia Gravis; ICD-10: G70.0)

In general, we do not annotate other vague or imprecise adjectives such as serio, importante, etc.:

E.g. eventos adversos <u>serios</u> Annotate only eventos adversos

E.g. *afectación neurológica importante* Annotate only *afectación neurológica*

Adjetives or past participles expressing possibility, probability, assertion, certainty or uncertainty, or disease activity:

activo confirmado posible probable sospechoso sugestiva susceptible

E.g. sepsis nosocomial <u>confirmada</u> o altamente <u>probable</u> Annotate only sepsis nosocomial.

E.g. *tuberculosis* <u>activa</u> Annotate only *tuberculosis*.

Adjetives specifying the type of measurement or average values measured: we annotate them if a concept (CUI) exists in the UMLS:

medio:

E.g. *presión arterial media* (C0428886 Mean blood pressure)

E.g. volumen corpuscular medio (C0863148 Mean corpuscular volume analyses, PROC)

promedio:

E.g. *presión arterial promedio* (C0428886 Mean blood pressure, PROC)

Adjetives specifying the average values of measurements: we do not annotate them if an UMLS CUI does not exist:

medio

E.g. *pérdida de peso <u>media</u>* (annotate only *pérdida de peso*)

promedio

E.g. *IMC* <u>promedio</u> (annotate only *IMC*)

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