

Annotation guidelines for the PHAEDRA corpus

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1	Introduction.....	4
2	Detailed guidelines.....	4
2.1	Entity annotation.....	4
2.1.1	General Guidelines	4
2.1.1.1	Annotation scope	4
2.1.1.2	Annotation span	5
2.1.2	Pharmacological_substance.....	6
2.1.2.1	Annotation Scope.....	7
2.1.2.2	Annotation span	10
2.1.3	Subject	12
2.1.3.1	Annotation scope	12
2.1.3.2	Annotation span	13
2.1.4	Disorder	14
2.1.4.1	Annotation scope	15
2.1.4.2	Annotation span	17
2.2	Relation Annotation.....	18
2.2.1	is_equivalent	19
2.2.1.1	Involved entities.....	19
2.2.1.2	Annotation scope	19
2.2.2	Subject_Disorder	20
2.2.2.1	Involved entities.....	20
2.2.2.2	Annotation scope	20
2.3	Event Annotation	21
2.3.1	Annotating negation cues for event annotation	23
2.3.1.1	Annotation Scope.....	23
2.3.1.2	Annotation Span.....	24
2.3.2	Annotating speculation cues for event annotation	25
2.3.2.1	Annotation Scope.....	26
2.3.2.2	Annotation Span.....	27
2.3.3	Annotating manner cues for event annotation	28
2.3.3.1	Annotation Scope	29
2.3.3.2	Annotation Span.....	29
2.3.4	Annotating relationships for event annotation	30
2.3.4.1	Coreference	30
2.3.5	Event annotation example sentences.....	34
2.3.6	General Guidelines	34
2.3.6.1	Annotation scope	34
2.3.6.2	Trigger Annotation.....	35
2.3.7	Combination	36
2.3.7.1	Possible participant Roles.....	36
2.3.7.2	Attributes	36
2.3.7.3	Annotation scope	37
2.3.7.4	Trigger Annotation.....	38
2.3.7.5	Participant Annotation.....	39
2.3.8	DDI.....	39

2.3.8.1	Possible participant roles.....	39
2.3.8.2	Attributes	39
2.3.8.3	Annotation scope	40
2.3.8.4	Trigger Annotation.....	41
2.3.8.5	Participant Annotation.....	41
2.3.9	Adverse_Effect.....	41
2.3.9.1	Possible participant roles.....	41
2.3.9.2	Attributes	42
2.3.9.3	Annotation scope	42
2.3.9.4	Trigger Annotation.....	44
2.3.10	Potential_Therapeutic_Effect	45
2.3.10.1	Possible participant roles.....	45
2.3.10.2	Attributes.....	46
2.3.10.3	Annotation scope	46
2.3.10.4	Trigger annotation	48
3	Guideline Summaries.....	50
3.1	Entity summary table	50
3.2	Relation summary table	54
3.3	Event summary tables.....	55
3.3.1	Combination.....	56
3.3.2	DDI.....	57
3.3.3	Adverse_effect	58
3.3.4	Potential_therapeutic_effect.....	59

1 Introduction

The annotation effort will be carried out in three stages. The first task is referred to as *entity annotation*. Entities are text spans that denote concepts of interest; the task consists of identifying and marking up entities, and assigning semantic labels to them, corresponding to entity categories. Secondly, in the *relation annotation* stage, certain types of links will be established between pairs of entities. In the third and final stage of the annotation, which we call *event annotation*, we will annotate associations (which we refer to as *Events*) between multiple entities, in order to capture complex pieces of information about interactions that revolve around drugs.

2 Detailed guidelines

2.1 Entity annotation

In the following sections, for each category of entity, we describe both the scope (i.e., the range of entities within each category that should be considered for annotation) and the span (i.e., the exact extent of text that should be marked up to represent entities with the category). Wherever possible, these descriptions are made as precise as possible, presenting illustrative examples of what should be *included* and *excluded* from the annotation scopes and spans.

In the examples provided, information that should be included within annotated text spans is shown inside square brackets, e.g., **[tyrosine]**. Emboldened spans correspond to the entities in focus in the specific examples; other entities of the same type in the same sentence that are related to the focussed examples may also be shown enclosed in square brackets, but are not emboldened.

Information that should be excluded from the annotated spans is crossed through, e.g., ~~[antimicrobial compounds]~~.

2.1.1 General Guidelines

2.1.1.1 Annotation scope

✓Include:

- All mentions of entities of the categories of the entities defined below. Even if the same entity is mentioned multiple times in a document, each individual mention should be annotated, regardless of whether it can be identified as a participant in an event.

Like [ibogaine] (40 mg/kg), **[18-MC]** (40 mg/kg) decreases the intravenous self-administration of [morphine] and [cocaine] and the oral self-administration of [ethanol] and [nicotine] in rats; unlike [ibogaine], **[18-MC]** does not affect responding for a nondrug reinforcer (water)

- Instances of abbreviations/acronyms as well as full forms of entities. Where an abbreviation/acronym follows a full form, both the acronym and full form should be annotated as separate entities.

[Neuroleptic malignant syndrome] ([NMS]) requires emergency treatment and can be fatal.

As the prevalence of [human immunodeficiency virus] ([HIV]) [infection] continues to rise the clinician is encountered with a diagnostic challenge

- Members of an entity class may vary from being very general to very specific. Where a sentence includes both a general member of the class and one or more enumerated specific instances, **both** the general class (underlined in the example below) and the more specific classes should be annotated.

Intravenous Adenocard (adenosine) has been effectively administered in the presence of other [cardioactive drugs], such as [quinidine], [beta-adrenergic blocking agents], [calcium channel blocking agents], and [angiotensin converting enzyme inhibitors]; without any change in the adverse reaction profile

✗Exclude:

- **Complete entities nested within longer entities (either of the same or different categories) should NOT be annotated** (but see note in the *Annotation Span* section below about annotation of discontinuous spans).

The profound influence of this drug on the immune system has raised questions concerning the emergence of [secondary [neoplasms]] after its use.

2.1.1.2 Annotation span

✓Include:

- Only include words that form an integral part of the entity name within the annotation span.
- Entities on either side of a slash (e.g., as alternatives/variations of a entity) should be annotated as two separate entities.

Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, [symptomatic hyperlactatemia]/[lactic acidosis], and peripheral neuropathy

✗Exclude:

- Modifiers in most cases (but see below for further examples for each entity category).

A liver biopsy in 2012 revealed **[marked fibrosis]**.

- Definite or indefinite articles (e.g. *a*, *the*) that may occur at the beginning of phrases

[The] fluoroquinolones for urinary tract infections: a review.

- Coordinating conjunctions, such as *and* or *or*. Each entity mentioned within a coordinated phrase should usually be annotated separately. However, in some coordinated phrases, certain parts of the coordination may not constitute entities by themselves. In this case, **discontinuous spans** may be used (the brat annotation tool has special facilities for annotating such spans).

In the example below, there are two distinct disorders. The meaning of this conjunction is *allergic reactions or hypersensitivity reactions*, although the word *reactions* only occurs in the second part of the conjunction. To make the correct meaning explicit in the annotation, the following strategy should be used:

- The phrase *hypersensitivity reaction* is annotated as a continuous span
- The words *allergic* and *reactions* are annotated as two separate parts of a discontinuous span.

Patients with HACA titers may have **[allergic] [or] [hypersensitivity [reactions]]**.

NOTE: Although the second part of the discontinuous span, i.e., *reactions*, is embedded within the longer, continuous span, *hypersensitivity reactions*, this is a different case to the one highlighted above in the *Annotation Scope* section, which stated that complete entities embedded within longer entities should not be annotated. Here, the embedded word forms only part of the complete discontinuous annotation, with the other part, i.e., *allergic*, occurring outside of the span *hypersensitivity reactions*.

2.1.2 Pharmacological_substance

All mentions of pharmacological substances mentioned in the text should be annotated.

These include:

- Pharmacological substances approved for human use, using generic names or brand names
- Active substances that are susceptible to interaction, but not currently authorised for any medical purpose for humans. Such substances include the following:
 - Drugs that were approved in the past but may have been withdrawn.
 - Experimental drugs, i.e., pharmacologically active substances tested in laboratory or clinical trials but not been approved for human use.
 - Veterinary drugs that have been approved for animal use **only**.
 - Toxins, i.e., substances produced by microbes, plants or animals and which are poisonous to other organisms. Often used in research for new drugs. Examples of toxins include cyanotoxins, dinotoxins, necrotoxins, neurotoxins, myotoxins and cytotoxins.

- Excipients - pharmacologically inactive ingredients used as a vehicle for administering an active substance.
- Metabolites that have pharmacological activity
- Expressions that refers to a group of drugs. Groupings may occur, e.g., according to their chemical, pharmacological or therapeutic properties of the drugs, or according to the organ or system on which they operate.

2.1.2.1 Annotation Scope

✓ Include:

- Expressions referring to genes or gene products where they are clearly being used as therapeutic agents

[**Echistatin**] alone had no effect on tyrosine phosphorylation in T24 cells, but dose-dependently inhibits the effects of [**contortrostatin**] when both are added simultaneously

- Expressions that correspond to generic drug names

Exposure to [**didanosine**] is increased when coadministered with [**tenofovir disoproxil fumarate**]

- IUPAC and IUPAC-like chemical names of drugs.

In rats, [**5-hydroxy-L-tryptophan**] decreased the initial absorption rate and increased AUC of gaboxadol

- Mentions of alcohol, when used synonymously with the drug *ethanol*.

The concomitant intake of [**alcohol**] and Acamprosate does not affect the pharmacokinetics of either alcohol or acamprosate

- Endogenous substances (i.e., substances that develop or originate within an organism) whose textual context indicates that they have been administered as exogenous drugs.

In adult diabetic patients under treatment with either sulfonylureas or [**insulin**] there is no change in the clinical effects of either tolmetin sodium or the hypoglycemic agents.

- Mentions of specific toxins.
 - We use the definition of toxin provided in Title 18 of the United States Code, which states that "... the term *"toxin"* means the toxic material or product of plants, animals, microorganisms (including, but not limited to, bacteria, viruses, fungi, rickettsiae or protozoa), or infectious substances, or a recombinant or synthesized molecule, whatever their origin and method of production".

The effects of anti-parkinsonian drug hemantane [(2-adamantyl)hexamethylenimine] (10 mg/kg, p. o.) and/or antibiotic drug doxycycline (100 mg/kg, p. o.), as well as that of neurotoxin [**1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine**] (**[MPTP]**) (4 x 20 mg/kg, i. p.) were studied in elevated plus maze test on C57BL/6 mice.

- Mentions of specific excipients.

The colchicine nanoemulsion was prepared with **[isopropyl myristate]**, eugenol, **[Tween80]**, ethanol and water, and eugenol was used as an oil phase in the formulation

- Generic or chemical names of metabolites.

The **[threohydrobupropion]** metabolite of bupropion does not appear to be produced by cytochrome P450 enzymes

- Words/expressions that refer to the brand names of drugs. These names usually start with a capital letter or may be completely written in upper case letters

Cytochrome P-450 is not known to be involved in the metabolism of **[Plenaxis]**

[DIAMOX] modifies phenytoin metabolism with increased serum levels of phenytoin

- Names of groups of drugs or other active substances

The **[fluoroquinolones]** are a rapidly growing class of **[antibiotics]** with a broad spectrum of activity against gram-negative and some gram-positive aerobic bacteria

The intensity, uniformity and time course of **[anticoagulant]** interference by [phenobarbital], [secobarbital], [glutethimide], [chloral hydrate] and [methaqualone] were systematically investigated in 16 patients receiving coumarin therapy

[Flavanoids] (including [flavanols], [flavones], [flavanones], and others) are potent **[antioxidants]** capable of inducing nitric oxide-dependent vasodilation, as well as having antiplatelet and anti-inflammatory effects

- Expressions that characterise general classes of drugs.
 - Often, such expressions precede or follow names of specific drugs in the class

Differential regulation of tyrosine phosphorylation in tumor cells by [contortrostatin], a **[homodimeric disintegrin]**, and **[monomeric disintegrins]** [echistatin] and [flavordin]

- Sometimes the name of the more general class of drugs immediately precedes the more specific drug as part of the same phrase. In such cases, the group and individual drug should be annotated separately

Using in situ hybridization, we observed that [METH] caused a rapid and transient dose-dependent increase in arc mRNA level in the striatum and cortex that was abolished by pretreatment with the specific **[dopamine D1 receptor antagonist]** [SCH-23390]

The effects of anti-parkinsonian drug hemantane [(2-adamantyl)hexamethylenimine] (10 mg/kg, p. o.) and/or antibiotic drug doxycycline (100 mg/kg, p. o.), as well as that of

[neurotoxin] [1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine] ([MPTP]) (4 x 20 mg/kg, i. p.) were studied in elevated plus maze test on C57BL/6 mice.

XExclude:

- Food
- Drink
- Names of specific alcoholic beverages (NOTE: Mentions of alcohol **should be annotated** when used synonymously with the drug *ethanol*).
- Environmental chemicals
- Vague or non-specific references to pharmacological substances

These [drugs] include the [thiazides] and other [diuretics], [corticosteroids], [phenothiazines], [thyroid products], [estrogens], [oral contraceptives]

- Chemical formulas of active substances.

Palytoxin (PTX), [C₁₂₉H₂₂₃N₃O₅₄], a highly toxic substance isolated from zoanthids of *Palythoa tuberculosa*, inhibited [(Na,K)-ATPase] ([ATP phosphohydrolase], EC 3.6.1.3) prepared from guinea pig heart and hog cerebral cortex in a dose-dependent manner at concentrations greater than 10⁻⁸ M.

- Names of specific alcoholic drinks.
- Mentions of alcohol that refer to the group of alkyl compounds containing a hydroxyl group.

An increase in serum osmolality and serum osmolal gap with or without high-anion-gap metabolic acidosis is an important clue to exposure to one of the [toxic alcohols], which include [methanol], [ethylene glycol], [diethylene glycol], [propylene glycol], or [isopropanol]

- Endogenous substances (i.e., substances that develop or originate within an organism), whose textual context denotes that the endogenous substance is being referenced (rather than exogenous administration of it in a therapeutic context).

[Thiazides] are known to induce hypercalcemia by the reduction of [calcium]-excretion in urine

- Mentions of water and saline as excipients.

The colchicine nanoemulsion was prepared with [isopropyl myristate], [eugenol], [Tween80], ethanol and [water], and eugenol was used as an oil phase in the formulation

- Common names of metabolites.

Metabolism of ketamine to its [N-demethylated metabolite] by liver homogenates in vitro was more rapid when the livers were obtained from ketamine pretreated rats.

- Appositive expressions describing the *function* of a specific drug

[Itraconazole], a ~~[potent inhibitor of P-glycoprotein]~~, moderately increases plasma concentrations of oral morphine. Individual variation in opioid response is considerable, partly due to pharmacokinetic factors

2.1.2.2 Annotation span

✓ Include:

- Where substance names are joined by hyphens (e.g., when an interaction between them is described), each substance should be annotated separately.

[Oseltamivir]-[warfarin] interaction in hypoplastic left heart syndrome: case report and review

- Descriptive information about the properties of the substance should be included in the annotation span, if it is considered to be part of the drug name.

In clinical trials, the safety profile in subjects treated with [Acamprosate] concomitantly with [anxiolytics], [hypnotics] and [sedatives] (including [benzodiazepines]), or **[non-opioid analgesics]** was similar to that of subjects taking placebo with these concomitant medications

- Where the drug is formulated as a salt, and the specific ion is specified, include this within the annotated span.

The CNS depressant effects of **[oxycodone hydrochloride]** may be additive with that of other [CNS depressants].

- Words that frequently occur at the end of expressions denoting groups of drugs. These include general words such as *agent* and *drug*, as well as words that denote the function of the drug, such as *agonist*, *antagonist*, *inhibitor*, *blocker*, *preparations*, *stimulants*, etc.

[Barbiturates] and [glutethimide] should not be administered to patients receiving **[coumarin drugs]**.

These medications have included [heparin], [warfarin], **[beta-adrenergic receptor blockers]**, **[calcium channel antagonists]**, **[angiotensin converting enzyme inhibitors]**, [intravenous] and [oral [nitrates]], [ticlopidine], and [aspirin].

- Words such as *products*, which may follow anatomical entities or disorders to refer to a drug used in the treatment of the disorder or problems with the anatomical entity.

These drugs include the [thiazides] and other [diuretics], [corticosteroids], [phenothiazines], **[thyroid products]**, [estrogens], [oral contraceptives]

- Adjectives (such as *atypical*), when they are required to fully characterise the group of drugs

we observed that [METH] caused a rapid and transient dose-dependent increase in arc mRNA level in the striatum and cortex that was abolished by pretreatment with the specific [dopamine D1 receptor antagonist] [SCH-23390] but not by an **[atypical neuroleptic]** [clozapine].

XExclude:

- Words that may be attached to drug names with hyphens, indicating their effects.

Health care practitioners should be aware of the possibility of [duloxetine]-**[induced]** hyponatremia, particularly in patients treated with [thiazide diuretics].

- Dosage information

Case 1 was a schizophrenic male with a history of NMS under treatment with [aripiprazole] **[20 mg]**

- Information about administration route or form

[Diltiazem]: Pretreatment of healthy volunteers with 30 mg or 90 mg t.i.d. [diltiazem] **[p.o.]** increased the AUC of [nifedipine] after a single dose of 20 mg [nifedipine] by factors of 2.2 and 3.1, respectively

It is concluded that [chloral hydrate] and [methaqualone] may be administered safely without additional caution in prothrombin test monitoring during **[oral]** [anticoagulant] therapy

- Words or expressions referring to therapy using the drug

He was subsequently placed on [oseltamivir] **[therapy]** according to the Centers for Disease Control and Prevention clinical practice guidelines.

- Where a drug is formulated as a salt, and the salt or salts are referred to generically (i.e. without using a specific ion name), exclude the generic reference from the annotated span.

This time to peak levels is identical to the time measured when [quinidine] **[salts]** are administered orally.

2.1.3 Subject

An organism, cell line, bacterium or group thereof, whose characteristics are under discussion. The organism may be human or otherwise.

2.1.3.1 Annotation scope

✓ Include:

- General references to groups of subjects or specific classes of subjects.

This case represents a drug-drug interaction that has not been previously reported in **[children]** or **[adolescents]**

- Names of specific species under discussion

The effects of DCG-IV and L-CCG-1 upon phencyclidine (PCP)-induced locomotion and behavioral changes in **[mice]**.

Effects of flavonoids isolated from *Scutellariae radix* on cytochrome P-450 activities in **[human]** liver microsomes.

- Names of bacteria under discussion

Synergism was observed when GL was combined with cefazolin against **[Bacillus subtilis]** and **[Klebsiella oxytoca]**.

- **ONLY** annotate vague references to subjects (using word such as *subjects* or *patients*) that do not include information about their characteristics under the following circumstances:

- when accompanied by information about the number of subjects

The intensity, uniformity and time course of anticoagulant interference by phenobarbital, secobarbital, glutethimide, chloral hydrate and methaqualone were systematically investigated in **[16 patients]** receiving coumarin therapy

- when reference is made to a subgroup of subjects

DIFFERIN Gel has the potential to produce local irritation in **[some patients]**.

- when information about disorders suffered by the subjects(s) are mentioned in close proximity, to further characterise the patients.

NOTE: The disorder should be separately annotated and **excluded** from the annotated *Subject* span. The *Subject* and *Disorder* spans should be linked via a *Subject-Disorder* relation, see below)

Lupus-like syndrome caused by 5-aminosalicylic acid in **[patients]** with inflammatory bowel disease

A **[[50-year-old]** diabetic and hypertensive **[male patient]]** is reported who had ticlopidine-induced marrow aplasia

✗Exclude:

- Vague references to subjects (using word such as *subjects* or *patients*) that do not include information about their characteristics or number.

[Patients] treated with 5-ASA compounds who experience acute inflammatory symptoms

2.1.3.2 Annotation span

✓Include:

- Characteristics of the subjects (e.g., sex, age, race)

The effects of combined administration of bombesin and verapamil hydrochloride (verapamil), a calcium channel blocker, on the incidence of peritoneal metastasis of intestinal adenocarcinomas induced by azoxymethane (AOM) and the labeling index of intestinal cancers were investigated in **[male Wistar rats]**.

A **[73-year-old African American man]** was diagnosed with hepatitis C in 2004, and had decided to not initiate therapy

- The number of subjects

The intensity, uniformity and time course of anticoagulant interference by phenobarbital, secobarbital, glutethimide, chloral hydrate and methaqualone were systematically investigated in **[16 patients]** receiving coumarin therapy

- Adjectives denoting that subjects do not have a disorder (often mentioned to contrast with those subjects who do have a disorder).

The increase in exposure to nifedipine by cimetidine was accompanied by relevant changes in blood pressure or heart rate in **[normotensive subjects]**.

A third study evaluated the potential interaction of once weekly dosing of fluconazole 300 mg to **[21 normal females]** taking an oral contraceptive containing ethinyl estradiol and

norethindrone

Quinidine is a substrate of CYP3A and has been shown to inhibit CYP3A in vitro. Coadministration of multiple doses of quinidine sulfate, 200 mg t.i.d., and nifedipine, 20 mg t.i.d., increased Cmax and AUC of nifedipine in **[healthy volunteers]** by factors of 2.30 and 1.37, respectively.

- References to a subset of subjects

The individual AUC values of norethindrone decreased very slightly (<5%) in **[3 of the 21 subjects]** after fluconazole treatment.

✗Exclude:

- Adjectives referring to disorders that characterise the subjects. Such adjectives should be separately annotated as *Disorder*, and linked with the subject via a *Subject-Disorder* relation, see below.

Case 1 was a **[schizophrenic male]** with a history of NMS under treatment with aripiprazole 20 mg

Two studies investigated the impact of coadministered cimetidine on blood pressure in **[hypertensive subjects]** on nifedipine.

2.1.4 Disorder

An observation about a medical subject's body or mind that is considered to be abnormal or caused by a disease, pharmacological substance or DDI. These may include (but are not limited to):

- pathologic functions
- neoplastic processes
- diseases or syndromes
- mental or behavioural issue
- cell or molecular dysfunction
- congenital, acquired or anatomical abnormality
- injury or poisoning
- viruses/bacteria
- signs & symptoms
- abnormalities in clinical attributes or measurements

The Medical Dictionary for Regulatory Activities (MEDDRA) may be used as an aid to help to determine when a phrase should be considered as a disorder. It can be accessed via BioPortal (<http://bioportal.bioontology.org/ontologies/MEDDRA>).

2.1.4.1 Annotation scope

✓ Include:

- Expressions that denote medical conditions

In 2006, he was diagnosed with **[deep vein thrombosis]** and **[pulmonary embolism]** and was started on warfarin

His **[hepatitis C]** treatment was discontinued at week 39 of the intended 48 weeks of treatment due to severe **[thrombocytopenia]**.

- Expressions indicating mental or behavioural dysfunction

The **[behavioral changes]** of mice induced by acute and repeated i.p. injection of phencyclidine (PCP) were observed by measuring locomotor activity and **[stereotyped behavior]**

18-MC, a novel iboga alkaloid congener, is being developed as a potential treatment for multiple forms of **[drug abuse]**.

- Expressions denoting an abnormality in a physiological function

The effects of DCG-IV were very strong and completely depressed the PCP-induced **[hyperlocomotion]**.

Serotonin syndrome is a syndrome identified by a triad of altered mental status, **[neuromuscular overactivity]**, and **[autonomic instability]** caused by the overstimulation of serotonin in the central nervous system and periphery.

- Expressions referring to neoplastic processes

The effects of combined administration of bombesin and verapamil hydrochloride (verapamil), a calcium channel blocker, on the incidence of **[peritoneal metastasis]** of **[intestinal adenocarcinomas]** induced by azoxymethane (AOM) and the labeling index of **[intestinal cancers]** were investigated in male Wistar rats

- Expressions referring to pathological processes

A liver biopsy in 2012 revealed marked **[fibrosis]**.

- Expressions referring to damage to an anatomical entity caused by disease or drugs

Ibogaine produces [whole body tremors] and, at high doses (> or = 100 mg/kg), **[cerebellar damage]**.

- Signs or symptoms caused by a medical condition/disease or induced by a drug or DDI

Both ibogaine and 18-MC ameliorate opioid **[withdrawal signs]**.

Ibogaine produces **[whole body tremors]**

[Disorientation] and [nausea] were improved after correction of [hyponatremia].

- Expressions referring to sets of signs or symptoms

[Serotonin syndrome] caused by fentanyl and methadone in a [burn] injury

- Abnormalities or changes in clinical attributes, measurements or anatomical entities that can be considered to constitute disorders, and which are expressed as noun phrases in one of the following ways:
 - Using prefixes such as *hypo* or *hyper*.
 - The names of measurements or anatomical entities are preceded by adjectives or nouns denoting abnormalities or changes. Such phrases should *only* be annotated as disorders in cases where the complete phrase can be understood to refer to a specific disorder. Please make use of MEDRDA, along with your own intuition, to help to make this decision.

Laboratory findings revealed hyponatremia, [hypo-osmolality], [concentrated urine], and [increased urine sodium]

Recent data suggest that self-reported acetaminophen use is associated with increased risk of cardiovascular events and a [rise in arterial blood pressure] (BP)

The increase in exposure to nifedipine by cimetidine was accompanied by relevant [changes in blood pressure] in normotensive subjects

Patients taking Acamprosate concomitantly with antidepressants more commonly reported both [weight gain] and [weight loss], compared with patients taking either medication alone

[Elevated prothrombin levels] were reported when the drug was administered

- Expressions referring to injury, poisoning or toxicity

Increased exposure may cause or worsen didanosine-related [clinical toxicities], including [pancreatitis], [symptomatic hyperlactatemia]/[lactic acidosis], and [peripheral neuropathy]

- Expressions referring to viruses or bacteria

Among fifteen species of bacteria tested, the antimicrobial activity of GL was the most potent against [Micrococcus luteus] (MIC, 0.75 mg/ml).

XExclude:

- Changes to clinical attributes, measurements or anatomical entities that are described using verbs

Acetazolamide may [~~increase blood glucose levels~~].

- Do not separately annotate disorders that occur within longer disorder spans – only annotate the longer span.

A patient that received methadone for **[[cancer]-associated pain]** developed **[myoclonus]** as a side effect

2.1.4.2 Annotation span

✓Include:

- Anatomical locations, when they form part of the name of the disorder.

These agents, including norfloxacin, ciprofloxacin, ofloxacin, enoxacin, and lomefloxacin, have been extensively studied and have demonstrated efficacy and safety profiles comparable to those of other traditional agents for the treatment of complicated or uncomplicated **[urinary tract infections]** and **[prostatitis]**.

In 2006, he was diagnosed with **[deep vein thrombosis]** and **[pulmonary embolism]** and was started on warfarin

This **[neurocutaneous syndrome]** consists of **[angiomas of the skin]**

An 81-year-old man with a history of **[[neoplasies of the] colon]** and **[prostate]** and anticoagulant treatment was referred for treatment of an **[ocular surface neoplasia]** on his left eye.

- Modifiers that have a specific medical meaning when attached to a condition, and can thus be considered part of the condition name

[Chronic hepatitis C] is a leading cause of severe **[liver disease]**

[Progressive paraplegia] has been attributed to **[spinal cord toxicity]**

Intravenous administration of levodopa ameliorated a **[refractory akathisia]** case induced by interferon-alpha

- Modifiers of the noun “effects” (or a synonym) that refer to a disorder. The modifier may be expressed as a noun or an adjective. The word “effects” (or its synonym) should be excluded from the annotated span.

The significant **[hyper locomotive]** effects of PMMA (30 mg/kg) compared to saline treatment were not, however, suppressed by pretreatment with the dopamine D2 receptor antagonist sulpiride or the 5-HT₂ receptor antagonist ketanserin.

- Disorders that are expressed as adjectives

Case 1 was a **[schizophrenic]** male with a history of [NMS] under treatment with aripiprazole 20 mg

✗Exclude:

- Modifiers referring to the severity of the disorder that are not considered part of the condition name

A liver biopsy in 2012 revealed **[marked]** [fibrosis].

[Consciousness change], **[modest]** [elevation of creatine kinase], and [leucocytosis] were the most consistent findings.

[Chronic hepatitis C] is a leading cause of **[severe]** [liver disease]

[Palmar-plantar erythrodysesthesia] ([PPE]) is an uncommon cutaneous complication of cytotoxic chemotherapy which generally presents as a **[painful]** [erythema]

- Modifiers that provide information about the cause or origin of a condition

The effects of DCG-IV were very strong and completely depressed the **[PCP-induced]** [hyperlocomotion].

- General expressions that do not refer to any specific disorders

This is a reminder of the importance of earlier detection of the **[soft signs]** and atypical features of [NMS] under this combined treatment.

2.2 Relation Annotation

In text, pairs of entities can sometimes be understood to be related to each other in specific ways. We wish to identify several such types of relationships.

The relationships to be identified fall into two categories:

- a) Those that should be annotated in all cases where the specified relationship is understood to hold.
- b) Those that should only be annotated in the context of event annotation.

In this section, we cover two types of relationships that fall under the first category; a further event-dependent relationship (co-reference) is covered in the section on events below.

In the examples, colour coding as used to denote the different entities involved, as defined in the *Involved entities* section for each relation type.

2.2.1 is_equivalent

It is sometimes the case that a sentence will introduce an alternative name or form for an entity. This could be, for example:

- A full entity name and its short form or acronym
- A generic drug name and its corresponding brand name

2.2.1.1 Involved entities

	Entity 1	Entity 2
Entity Type	Any	Any (but sharing the same category as Entity 1)

2.2.1.2 Annotation scope

✓ Include:

- Link **alternative** forms/names of the same entity that are mentioned within **the same sentence**

As **immediate-early genes** (**IEGs**) are thought to play a critical role in mediating stimulus-induced neural plasticity

Intravenous **Adenocard** (**adenosine**) has been effectively administered in the presence of other cardioactive drugs

✗ Exclude:

- **Do not** link **duplicate mentions of the same form an entity** that occur multiple times in a sentence

As immediate-early genes (**IEGs**) are thought to play a critical role in mediating stimulus-induced neural plasticity, **IEG** response induced by methamphetamine (METH) has been characterized to define the changes in gene expression that may underlie its long-lasting behavioral effects.

2.2.2 Subject_Disorder

Individual or groups of subjects may be characterised according to the disorder from which they suffer. In such cases, the annotated *Subject* and *Disorder* spans should be linked using a *Subject_Disorder* relation.

2.2.2.1 Involved entities

	Entity 1	Entity 2
Entity Type(s)	Subject	Disorder

2.2.2.2 Annotation scope

✓ Include:

- Link any disorder that is used specifically to characterise an introduced subject or group of subjects, and which occurs in the same sentence. Typical ways in which this information is expressed include the following:
 - The disorder occurs in close proximity to the *Subject* annotation, often following a phrase such as *with* or *suffering from*

Lupus-like syndrome caused by 5-aminosalicylic acid in **patients** with **inflammatory bowel disease**.

- The disorder is expressed as an adjective, preceding the *Subject* annotation

Case 1 was a **schizophrenic male** with a history of NMS under treatment with aripiprazole 20 mg

- The disorder is expressed as an adjective in the middle of the *Subject* annotation (in this case, the *Subject* should have been annotated as a discontinuous span)

A **50-year-old diabetic male patient** is reported who had ticlopidine-induced marrow aplasia

- If two different (groups of) subjects are mentioned, each characterised by a different disorder, then as many *Subject* annotations should be created as there are different (groups of) subjects, and a Subject-Disorder relation should be created for each subject annotation. Consider the following sentence:

Methotrexate reduce the incidence of CNS and systemic relapses in children with acute lymphoblastic leukemia or stage III lymphoblastic lymphoma

In the above sentence, there are two distinct groups of subjects, i.e.

- *children with acute lymphoblastic leukemia*
- *children with stage III lymphoblastic lymphoma*

To annotate information about the two groups of subjects, **2 different** Subject annotations should be created over the word *children*. Then, the first of these should be linked via a *Subject-Disorder* annotation to *acute lymphoblastic leukemia*, and the second Subject annotation should be linked via a *Subject-Disorder* annotation to *stage III lymphoblastic lymphoma*.

XExclude:

- **Do not** link disorders that are not used to provide a specific characterisation of a subject or group of subjects, even when they occur in the same sentence

Patients treated with acebutolol plus catecholamine depletors should, therefore, be observed closely for evidence of marked **bradycardia** or **hypotension**

2.3 Event Annotation

In addition to simple links between pairs of entities as described in the *Relation* annotation section described above, entities can be related to each other in different, more complex ways to create larger chunks of information. Consider the following sentence snippet:

[DIFFERIN] Gel has the potential to produce local [irritation] in [some patients].

There are three entities annotated in the example, i.e.:

1. *DIFFERIN* - Pharmacological_substance
2. *irritation* - Disorder
3. *some patients* – Subject

Based the other words in the sentence, and the way that they are arranged/structured, we can understand that these entities are involved in (or *participate in*), the description of a specific piece of information, i.e., that DIFFERIN may produce an adverse reaction (namely *irritation*) in certain subjects.

We refer to such pieces of information as *Events*, and to the entities involved as *participants* of the event. Some further points to note about the event include the following:

- As a whole, the event conveys a particular type of information, i.e., it describes the potential effect of the named drug, or, more specifically, it describes the adverse effect that may be caused by the drug
- The different participating entities contribute different types of information towards the overall description of the event, i.e.,
 - *DIFFERIN* is the entity responsible for the occurrence of the adverse, i.e., it (potentially) causes the irritation to manifest itself.
 - The disorder *irritation* is the entity affected by or resulting from the use of DIFFERIN

- The *Subject* phrase *some patients* conveys the fact that the adverse effect only occurs in certain subjects
- The different participants can be understood to be linked together through their relationship to a particular word in the sentence (i.e., *produce*). This word, called the event *trigger*, also partly characterises the nature or meaning of the event.

The event annotation task consists of identifying **all** occurrences of events in text belonging to a fixed set of semantic types, which are fully defined below. Specifically, annotation of events consists of the following subtasks:

- **Identifying a suitable trigger word or phrase for the event, and assigning a semantic category corresponding to one of the event types introduced below**, which characterises the type of information expressed by the event as a whole. According to the types defined below, *produce* is assigned the event type *Adverse_effect*.
- **Identifying the participants of the event that occur in the same sentence as the trigger, and assigning labels (called *semantic roles*), according to the general type of information that they contribute towards the event.** A fixed set of potential semantic roles is defined for each event type. In the above example, the following semantic roles are assigned to the participants
 - *DIFFERIN* – *has_agent*
 - *irritation* - *affects*
 - *some patients* – *has_subject*

NOTES:

- A given semantic role may be used more than once for each event, e.g., it is possible to assign the *has_agent* role to multiple entities for a given event annotation, if there are multiple causes
- Only information that is provided in the sentence containing the event should be used as evidence for annotating the event and its participants (i.e., implicit information that can only be understood by considering other sentences should not be used).
- **Assigning values to attributes that characterise the interpretation of the event.** For example, the interpretation of an event becomes different if it is negated, i.e., it is being reported as something that does not take place. Further details about each of these attributes are provided in the sections below.

Event annotation thus consists of (1) identifying multiple spans of text, which are labelled and linked together in different ways, according to their function within the description of the event, and (2) assigning values to attributes that take note of how the event should be interpreted.

NOTE: All instances of events of the types introduced below should be annotated, even if the same event is mentioned more than once in a sentence.

2.3.1 Annotating negation cues for event annotation

In certain cases, the meaning of an event is negated. Consider the following example:

There was **no** reaction *associated* with thioridazine and/or haloperidol.

The word *no* is used to convey the fact that the *Adverse_effect* denoted by the trigger *associated* **did not take place**, i.e., the administration of neither thioridazine nor haloperidol caused a reaction to occur.

We wish to make a distinction between events that are stated (or assumed) to be true and those that are explicitly stated as being false. As detailed below, events have a *Negated* attribute, which is selected in cases where there is explicit evidence in the sentence that the event should be negated. In such cases, there will usually be a word or phrase in the sentence that explicitly denotes the negation (as in the case for *no* in the above example).

Whenever an event is clearly negated, we wish to annotate the negation-indicating phrase, and assign a special category to it, i.e., *Negation_cue*. Such phrases are then linked to the event using a special semantic role label, i.e., *has_cue*. Below, we provide an indication of the annotation scope and span selection guidelines for the *Negation_cue* category.

(NOTE: To help to emphasise the points made below, event triggers are denoted using a **red background**, while negation cues are denoted using a **yellow background**. Please refer to the detailed event annotation guidelines below for details about how event triggers should be annotated).

2.3.1.1 Annotation Scope

✓ Include

- Only annotate negation cues when they are clearly used to negate events.

There was **no** reaction **associated** with thioridazine and/or haloperidol.

✗ Exclude:

- **Do not** annotate negation-indicating words or phrases when they are not used to negate an annotated event in the sentence

A 73-year-old African American man was diagnosed with hepatitis C in 2004, and had decided to **not** initiate therapy

- **Do not** annotate negation-indicating words when they form part of a longer phrase that conveys a different type of information

In the example below, the word *not* is part of the larger phrase *not significant*. As such, this **does not** denote that the described DDI did not take place, but rather that it took place with a low level of intensity. Indeed, the phrase *not significant* should be annotated a Manner cue (see section below).

The interaction **effects** of RLX and ALN were **not** significant.

In the example below, the word *never* is part of the longer phrase *never previously*. From the context of the sentence, it can be understood that an association between the drugs *oxaliplatin* and *5-fluorouracil regimens*, and *pulmonary adverse reaction* has now been observed, even though it has not been previously. Hence, the event **should not** be negated.

It is concluded that the aforementioned pathological manifestations were due to chemotherapy and included a pulmonary adverse reaction, a feature **never** previously **associated** with oxaliplatin and 5-fluorouracil regimens

2.3.1.2 Annotation Span

✓ Include

- Inherently negative words, such as *no* and *not*, where these can be understood to directly negate the event.

Population pharmacokinetic analyses revealed that TNF blocking agents did **not** **influence** abatacept clearance

- Event triggers may include a co-spanning *Negation_cue* annotation, if the trigger itself denotes that the event did not take place (e.g. if the trigger denotes that a treatment was not shown to have an effect)

Although many cases are reported to recover with colony-stimulating factors and corticosteroids, others are **unresponsive**

2.3.2 Annotating speculation cues for event annotation

In other cases, the context of an event may show that there is some degree of uncertainty or speculation as to whether it will actually take place. Consider the following example:

Reproductive toxicology studies have revealed no evidence of impaired fertility due to AMEVIVE

Looking at the end of the above sentence, the phrase *impaired fertility due to AMEVIVE* appears to denote an *Adverse_drug_effect*, i.e., the drug AMEVIVE causes the condition *impaired fertility* to occur. However, looking immediately to the left of this phrase, we see the phrase *no evidence*, which means that it is **highly likely** that AMEVIVE *does not* cause impaired fertility, according to the results of the reproductive toxicology studies mentioned. By using the phrase *no evidence*, the author(s) are not committing to the fact that AMEVIVE definitely does not cause impaired fertility. Rather, they are expressing a high degree of speculation towards the truth of the event, based upon the lack of evidence in the experimental data that they have to hand.

We wish to distinguish between expressions of negation and expressions of uncertainty towards an event. The level of uncertainty could vary between slight speculation (using a word such as *may*) and more extreme speculation, as in the example above, where the high degree of uncertainty comes very close to negation.

However, in this annotation effort, we treat negation and speculation as two separate attributes of the interpretation of an event. To understand why, consider the following example:

In the presence of these methylxanthines, adenosine may not be effective.

In the above sentence, while the word *may* expresses uncertainty, the uncertainty is actually towards a negated event (denoted through the additional presence of the word *not*).

Whenever an event is speculated or uncertain to any degree, we wish to annotate the speculation-indicating phrase, and assign a special category to it, i.e., *Speculation_cue*. Such phrases are then to be linked to the event using the special semantic role label, i.e., *has_cue*. Below, we provide an indication of the annotation scope and span annotation guidelines for the *Speculation_cue* category.

(NOTE: To help to emphasise the points made below, event triggers are denoted using a **red background**, while speculation cues are denoted using a **yellow background**. Please refer to the detailed event annotation guidelines below for details about how event triggers should be annotated).

2.3.2.1 Annotation Scope

✓ Include

- Annotate speculation cues that convey uncertainty about whether the event will actually take place

Health care practitioners should be aware of the possibility of duloxetine-induced hyponatremia, particularly in patients treated with thiazide diuretic

- Annotate cues that convey risk

Concurrent administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone

- Annotate cues denoting that the event may not take place all of the time

Flavordin alone was found to have no effect on CAS, but can completely block contortrostatin-induced phosphorylation of this protein in MDA-MB-435 cells.

- Annotate cues that indicate a lack of evidence/knowledge about the truth of the event.

Reproductive toxicology studies have revealed no evidence of impaired fertility due to AMEVIVE

Cytochrome P-450 is not known to be involved in the metabolism of Plenaxis

RLX+ALN reduced bone turnover more than either drug alone, resulting in greater BMD increment, but whether this difference reflects better fracture risk reduction was not assessed in this study.

XExclude:

- **Do not** annotate speculation-indicating words or phrases when they do not denote a speculated interpretation of an annotated event in the sentence

Although the pattern of use for oral allopurinol includes longer term therapy, particularly for gout and renal calculi, the experience gained **may** be relevant

2.3.2.2 Annotation Span

✓Include

- Words or phrases denoting possibility, probability or risk

The case described is the first report associated with fentanyl and methadone without the coadministration of other serotonergic agents, and a **possible** drug **interaction** with voriconazole is discussed

This raises awareness of using multiple serotonergic narcotics and the **potential** **precipitation** of serotonin syndrome

Increased exposure **may** **cause** didanosine-related clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy

Products containing calcium and other multivalent cations **likely** will **interfere** with absorption of alendronate

- According to the event-specific trigger annotation guidelines provided below, suitable triggers may convey both the presence of an event *and* the fact that the event is speculated. In this case, the same span of text may be annotated as *both* an event trigger and a *Speculation_cue*.

The **risk** of hypoglycemia secondary to this mechanism may be increased if allopurinol and chlorpropamide are given concomitantly in the presence of renal insufficiency.

Epoprostenol is being **evaluated** in other forms of pulmonary hypertension,

- Phrases indicating a lack of evidence or knowledge

Currently, there are **no identified** case reports of narcotics as the sole agent **causing** serotonin syndrome

The **effects** of aliskiren on warfarin pharmacokinetics have **not been evaluated** in a well-controlled clinical trial

- Annotate the **minimal span** required to convey the speculation

For prevention of CYP2E1-mediated bioactivation, depending on protoxicant disposition, a second DSF dose **might be** necessary to completely **prevent** toxicity

2.3.3 Annotating manner cues for event annotation

Sometimes, the context of an event provides information about rate, intensity, strength or level of significance of the event. We refer to this information as the *Manner* of the event. Consider the following example:

There is little if any clinically significant interaction between Acarbose and metformin

In this sentence, the phrase *little if any clinically significant* denotes that the intensity of the event denoted by the trigger *interaction* is very low. Although the level of interaction may be very small, this still has a different meaning to saying that the interaction did not take place at all. On the other hand, if the sentence was changed to the following, then it could be understood that the interaction took place with high intensity: *There is a highly significant interaction between Acarbose and metformin.*

We wish to identify events whose context indicates that the *Manner* of the interaction differs from what could be expected by default. For such events, we distinguish between events for which the Manner is *lower* than the default (in which case a value of *Low* is assigned) and events for which the Manner is *higher* than the default (in which case a value of *High* is assigned). In all other cases, the default *Neutral* value of *Manner* is assigned to events.

For all events with a *Manner* value of *Low* or *High*, there must be a word or phrase in the same sentence as the event that indicates the level or intensity. Such words/phrases should be annotated and assigned the special category *Manner_cue*. Depending on the type of manner expressed by the cue, the value of the *Manner* attribute for the event should then be set to either *Low* or *High*. Below, we provide an indication of the annotation scope and span annotation guidelines for the *Manner_cue* category.

(NOTE: To help to emphasise the points made below, event triggers are denoted using a **red background**, while speculation cues are denoted using a **yellow background**. Please refer to the detailed event annotation guidelines below for details about how event triggers should be annotated).

2.3.3.1 Annotation Scope

✓ Include

- Annotate all cues used to convey that fact that an event took place with a higher or lower level or rate of intensity than would be expected by default

There is **little if any clinically significant** **interaction** between Acarbose and metformin.
(**Manner=Low**)

Flavordin alone was found to have no effect on CAS, but can **completely** **block** contortrostatin-induced phosphorylation of this protein in MDA-MB-435 cells. (**Manner=High**)

- The level of significance of an event can also sometimes be conveyed by words and phrases that indicate its relative frequency (e.g, rare, few frequent, common, etc.)

Alopecia and hair loss are **rare** **side effects** of psychotropic drugs (MANNER=LOW)

2.3.3.2 Annotation Span

✓ Include

- Words or phrases denoting amount of change, increase or decrease

PGF2alpha produced **significantly** **increased** vasoconstriction (**Manner=High**)

- Words or phrases denoting level of significance or completeness of the event

concurrent administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and **no significant** additional **efficacy** over use of the TNF antagonists alone. (**Manner=Low**)

Catecholamine-depleting drugs, such as reserpine, may have an **additive** **effect** when given with beta-blocking agents (**Manner=High**)

The nephrosis **resolved** **almost completely** after immunosuppressive treatment. (**Manner=High**)

Our patient also **did not completely** **respond** to these medications (**Manner=Low**)

- Words or phrases denoting rate of the event

Flecainide overdose can **rapidly** **result** in profound cardiovascular collapse (**Manner=High**)

2.3.4 Annotating relationships for event annotation

In the context of event annotation, we define a further type of relationship that holds between pairs of text spans, in order to extend the possibilities of annotating meaningful events within the boundaries of a sentence.

Note that these relationships should only be annotated in conjunction with annotating events. That is to say that, when such relationships occur outside of the scope of events, then there is no need to annotate them.

2.3.4.1 Coreference

This relation type is used when a phrase that corresponds to an event participant is too general or unspecific to have been annotated during the entity annotation phase, but where it is clear from the context that the general phrase refers to a more specific entity or entities, which occur in a nearby sentence (**i.e., up to three sentences preceding or following the sentence in which the event occurs, although see below about annotating “chains” of co-reference**).

To make this more concrete, consider the following example (event trigger shown using a red background), which contains two sentences.

Certain drugs tend to produce hyperglycemia. These drugs include the thiazides and other diuretics.

In the first sentence, there is an *Adverse_effect* event, similar to the one introduced above. There is a trigger, *produced*, while *hyperglycemia* corresponds to the *affects* role of the event. Within the sentence, the phrase *Certain drugs* clearly plays the *has_agent* role within the sentence. However, since *Certain drugs* refers to an unspecified group of drugs, it will not have been annotated as a *Pharmacological_substance* entity during the entity annotation phase, because, as an expression in isolation, it is too vague.

However, by looking at the second sentence, we see that some more concrete examples of the groups of drugs referred to by the phrase *Certain drugs* are provided, i.e., *thiazides* and *diuretics*. According to the entity guidelines, these two groups will have both been annotated as *Pharmacological_substance* entities. In order to be able to fully capture the complete meaning of the event in the first sentence, it is meaningful to annotate *Certain drugs* as the *has_agent* role and to show that expression actually **corefers** to the two specific drug groups provided in the second sentence, i.e., the phrase is acting as a placeholder or shorthand to refer to these more specific phrases. To perform the event annotation in such cases, we carry out the following steps:

- We assign the special entity type **Coreferring_mention** to the general phrase that corresponds to an event participant, but which has not been annotated during the entity annotation phase. So, in the above example, *Coreferring_mention* would be assigned to the phrase *Certain drugs*. It is NOT necessary to additionally assign a more specific semantic category to the *Coreferring_mention* phrase. For instance, in the above example, the phrase *certain drugs* should ONLY be assigned the category *Coreferring_mention* and NOT *Pharmacological_substance*. The exact category of the co-referring mention can be inferred according to the other entities linked in the relationship (see next step).
- We identify the specific entities that the general *Coreferring_mention* phrase refers to, and we annotate pairwise relations of type *Co-reference* between the *Coreferring_mention* phrase and each of the entities to which it co-refers.
NOTE: It is permitted to annotate “co-reference chains” to allow vague event participants to be annotated throughout an abstract. If at least one *coreferring_mention* phrase can be linked to a more specific phrase within three sentences, then it is permitted to annotate and link other *coreferring_mention* phrases to each other, as long as each of them occurs within three sentences of each other. In this way, a chain of *coreferring_mention* phrases can be followed, until the specific entity phrase is reached.

2.3.4.1.1 Involved entities

	Entity 1	Entity 2
Entity Type(s)	Coreferring_mention	Any

2.3.4.1.2 Annotation scope

The *Coreference* relation should **only** be annotated under the following circumstances:

- The phrase to be annotated with the *Coreferring_mention* category should be in an **event-containing sentence**, and logically correspond to an **entity** (one of the three types annotated during the entity annotation phase described above) that is a **participant** of the event.
- The event participant phrase that is annotated as *Coreferring_mention* should not have been annotated as an entity during the entity annotation phase, because it is too general, according to the entity annotation guidelines.
- The general phrase annotated as a *Coreferring_mention* **clearly** refers to **one or more specific entities** in a nearby sentence which have been annotated as part of the entity annotation phase
- The more specific entities **MUST** occur within **three sentences (EITHER preceding OR following)** the sentence that contains the *Coreferring_mention* phrase.
- The *Coreferring_mention* category should be used **only for entities**; co-reference at the level of complete events should NOT be annotated

Returning to the example introduced above, two different coreference relations should be annotated, as illustrated below, since there are two groups of drugs to which the phrase *Certain drugs* refers.

Certain drugs tend to **produce** hyperglycemia and may lead to loss of blood glucose control. These drugs include the **thiazides** and other diuretics.

Certain drugs tend to **produce** hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other **diuretics**.

When the event is subsequently annotated, *Certain drugs* will be assigned the *has_agent* role of the *Adverse_effect* event with the trigger *produce*, and the coreference relation annotations will allow specific entities to be associated with this general phrase.

In the following example, the co-referring mention, i.e. *these medications*, refers to two drugs that were introduced in the previous sentence (rather than in the following sentence, as was

the case for the first example). Again, a *Coreference* relation is annotated between the co-referring mention and each of the drugs.

Although many cases are reported to recover with **colony-stimulating factors** and corticosteroids, others are unresponsive or partially responsive. Our patient also did not completely **respond** to **these medications**, but was successfully treated with cyclosporine alone

Although many cases are reported to recover with colony-stimulating factors and **corticosteroids**, others are unresponsive or partially responsive. Our patient also did not completely **respond** to **these medications**, but was successfully treated with cyclosporine alone

In the example below, the co-referring mention phrase, i.e., *symptomatology*, occurs more distantly from the NEs to which it refers. Although there are disorders mentioned in the sentence that immediately precedes the one containing *symptomatology*, it is actually the sentence before this one that refers to specific symptoms, and hence it is these that should be annotated as being co-referent with *symptomatology*.

The patient was readmitted with symptoms of **rhinorrhea**, poor feeding, and decreased activity level. She was found to have diffuse pulmonary infiltrates on chest radiograph and a marked peripheral eosinophilia without leukocytosis. After discontinuing captopril and starting systemic steroids, her **symptomatology** rapidly **improved**, and her eosinophilia and radiographic abnormalities both resolved.

The patient was readmitted with symptoms of rhinorrhea, **poor feeding**, and decreased activity level. She was found to have diffuse pulmonary infiltrates on chest radiograph and a marked peripheral eosinophilia without leukocytosis. After discontinuing captopril and starting systemic steroids, her **symptomatology** rapidly **improved**, and her eosinophilia and radiographic abnormalities both resolved.

The patient was readmitted with symptoms of rhinorrhea, poor feeding, and **decreased activity level**. She was found to have diffuse pulmonary infiltrates on chest radiograph and a marked peripheral eosinophilia without leukocytosis. After discontinuing captopril and starting systemic steroids, her **symptomatology** rapidly **improved**, and her eosinophilia and radiographic abnormalities both resolved.

Coreference relations **SHOULD NOT** be annotated when there is **no definite link** between the more general phrase and the more specific phrase. In the example below, the phrase *foreign substance* is stated as a very general cause of the disorder *serum sickness*. From the context, it cannot be determined definitely that *phenylbutazone* is considered to be a specific example of such a foreign substance.

Skin manifestations of a case of **phenylbutazone**-induced serum sickness-like reactions. Serum sickness consists of a systemic reaction resulting from the formation of soluble circulating immunocomplexes after the introduction of a **foreign substance** into the body.

2.3.5 Event annotation example sentences

For each category of events introduced below, several example sentences are provided. Trigger words/phrases are always shown with a **red background**. For each event type, a set of possible role types for the participants associated with the event type is provided, along with the background colour used to denote the roles of different participants in the examples.

IMPORTANT NOTES ABOUT EXAMPLE SENTENCES:

- 1) In each example sentence shown, we highlight only a single event and its participants. However, it may be the case that the example sentences contain other events, which are not highlighted. We have chosen to highlight only a single event in each case, to ensure that there is no confusion about which participants belong to which events.
- 2) Event participants can correspond either to entities or to other events. In the latter case, we refer to the event that plays the role of an event participant as an *embedded* event. In the example sentences, participants that correspond to embedded events are shown by highlighting only the trigger of this “embedded” event, with the background colour appropriate to the role that the participant event is playing in the “top-level” event. This will become clearer as the events are introduced below.

2.3.6 General Guidelines

2.3.6.1 Annotation scope

✓ Include:

- A fixed set of *potential* semantic roles is defined for each event type. The event should be annotated regardless of whether participants corresponding to *all* of the possible roles defined for the event type are present within the sentence (ALTHOUGH each event type includes a minimum set of participants that **MUST** be present in the sentence for the event to be annotated at all. These conditions are detailed in the descriptions of the individual event types below).
- Event participants can correspond either to entities or to other “embedded” events.

- If both the full form and short form/acronym of the same entity appear in the same sentence, then the full form should be annotated as the event participant.
- If a generic drug name and its associated brand name appear in the same sentence, then annotate the generic drug name as the event participant.

✗Exclude:

- Entities/other events that could be understood as semantically linked to the event trigger, but which do not correspond to one of the fixed set of semantic roles defined for the appropriate event type.

2.3.6.2 Trigger Annotation

✓Include:

- The length of event triggers should generally be kept to the minimum needed to characterise the event. The following general guidelines hold, although some specific examples/rules are provided below for individual event types.
 - Most typically a event trigger will correspond to a verb (e.g., *interact*) or a nominalisation of the verb (e.g., *interaction*)
 - In many cases, a trigger noun or verb is followed by a preposition or an adverb. In such cases, the exact text span to annotate as the trigger should be determined as follows:
 - If the verb/noun has a meaning that is distinct without the following preposition/adverb, then this preposition or adverb should be **excluded** from the annotation span. This would be the case, e.g., for *interact with*, *interaction between*, etc.
 - If the combination of noun/verb and following preposition/adverb can be seen to have a special meaning, then the preposition/adverb should be **included** in the annotation span. This is case for phrases such as *cut down*, *step up*, etc.
 - In cases where the trigger verb is in the passive form, e.g. *caused by*, then only the verb itself should be annotated (in this case, *caused*)
 - Depending on the type of event being annotated, other “fixed” phrases with specific meanings may act as triggers. Examples include *due to* and *in the presence of*. In this case, the **whole phrase** should be annotated as the trigger.
- The same trigger may be used to denote more than one event, when more than one distinct set of participants is specified in the sentence
- Where there are multiple words that could act as triggers for events, the most “informative” or specific word or phrase should be chosen as the trigger.

✗Exclude:

- Words or phrases expressing negation, manner or speculation should be **excluded** from the annotated trigger

A 50-year-old diabetic and hypertensive male patient is reported who had ticlopidine-induced marrow aplasia **partially responsive** to colony-stimulating factors and

corticosteroid

2.3.7 Combination

A specification **that two or more pharmacological substances** are being used at the same time (e.g., they have been co-administered).

2.3.7.1 Possible participant Roles

Role	Description	Possible types
has_participant	A pharmacological substance being combined/co-administered	Pharmacological_substance
has_cue	An indication that the event is negated and/or speculated, or which provides information about the manner of the event	Negation_cue Speculation_cue Manner_cue

2.3.7.2 Attributes

Attribute Name	Description	Possible values
<i>Negated</i>	Assigned if the interaction is negated	
<i>Speculated</i>	Assigned if there is some degree of speculation/uncertainty specified towards the process	
<i>Manner</i>	Provides information about the rate, level or intensity of the event	High Neutral (Default) Low

2.3.7.3 Annotation scope

✓ Include:

- Any mention of pharmacological substances being used in combination, regardless of whether any specific effect resulting from this combination is mentioned in the sentence. Such mentions could include:
 - One pharmacological substance being used in the presence of another

Compared to nifedipine monotherapy, blood pressure was lower in the presence of doxazosin.

- Concurrent administration/intake of two or more pharmacological substances

Concurrent administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone.

Catecholamine-depleting drugs, such as reserpine, may have an additive effect when given with beta-blocking agents

Patients treated with acebutolol plus catecholamine depletors should, therefore, be observed closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia.

- One or more pharmacological substances being taken after another

PGF2alpha produced significantly increased vasoconstriction after a single administration of oxytocin

✗ Exclude:

- Cases where there is explicit mention of interaction between the pharmacological substances. These should be annotated as the DDI event type (see next section)

Clinical implications of warfarin interactions with five sedatives.

- Cases where there are **less than two pharmacological substances** that can be linked as participants of the event in the sentence.

In this case, it was suspected that a combination of cigarette smoking, pulmonary fibrosis, and low-dose methotrexate-therapy might have promoted the development of lung cancer.

2.3.7.4 Trigger Annotation

✓Include:

- Trigger span should be sufficient to capture the nature of the relationship between the pharmacological substances.
- Trigger should ideally capture a meaning similar to “combination” or “taken/administered in combination”, depending on the wording of the sentence.
- At the minimum, a word or phrase denoting combined use should be annotated as the trigger

Patients treated with acebutolol plus catecholamine depletors should, therefore, be observed closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia

- If the combination is denoted by a phrase that is considered to be a “fixed” or standard phrase for denoting such a combination, then the whole phrase should be annotated as the trigger.

In normotensive subjects receiving single doses of 10 mg or multiple doses of up to 20 mg nifedipine t.i.d. alone or together with cimetidine up to 1000 mg/day, the AUC values of nifedipine in the presence of cimetidine were between 1.52 and 2.01 times those in the absence of cimetidine.

- If the word denoting the combination is preceded or followed by a word or phrase that denotes intake or administration, then this should be included within the annotated trigger span.

Some narcotics, including fentanyl and methadone, have these properties and may be associated with the development of serotonin syndrome when used in conjunction with other agents

The concomitant intake of alcohol and Acamprosate does not affect the pharmacokinetics of either alcohol or acamprosate.

Catecholamine-depleting drugs, such as reserpine, may have an additive effect when given with beta-blocking agents.

2.3.7.5 Participant Annotation

✓ Include:

- If it is specified that a particular pharmacological substance may be combined with one or more other pharmacological substances, then separate events should be annotated for each pairwise combination.

The majority of patients in RA clinical studies received one or more of the following **concomitant medications** with ORENCIA: MTX, NSAIDs and anakinra.

The majority of patients in RA clinical studies received one or more of the following **concomitant medications** with ORENCIA: MTX, NSAIDs and anakinra.

The majority of patients in RA clinical studies received one or more of the following **concomitant medications** with ORENCIA: MTX, NSAIDs and anakinra.

2.3.8 DDI

A specific mention that there is an interaction between **two or more** pharmacological substances. This is in contrast to the *Combination* event above, which simply specifies that two or more pharmacological substances have been combined, without explicit mention of whether they interact with each other.

2.3.8.1 Possible participant roles

Role	Description	Possible types
has_participant	A pharmacological substance involved in the interaction	Pharmacological_substance
has_cue	An indication that the event is negated and/or speculated, or which provides information about the manner of the event	Negation_cue Speculation_cue Manner_cue

2.3.8.2 Attributes

Attribute Name	Description	Possible values
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<i>Negated</i>	Assigned if the interaction is negated	
<i>Speculated</i>	Assigned if there is some degree of speculation/uncertainty specified towards the interaction	
<i>Manner</i>	Provides information about the rate, level or intensity of the event	High Neutral (Default) Low

2.3.8.3 Annotation scope

✓Include:

- Any explicit mention of an interaction between two or more pharmacological substances.

Clinical implications of warfarin interactions with five sedatives.

✗Exclude:

- Combinations of pharmacological substances that do not explicitly mention an interaction, even when there is explicit mention in the sentence that the combination has (or may have) some type of effect.
 - The combination of pharmacological substances should be encoded using the *Combination* event type (see above)

Concurrent administration of a TNF-antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone.

- Cases where less than two pharmacological substances involved in the interaction are mentioned.

To aid in the prediction of drug interactions with alprazolam, the human CYP involved in the 1'- and 4-hydroxylation of alprazolam were characterized using human liver microsomes

2.3.8.4 Trigger Annotation

✓Include:

- Triggers for DDI events will mostly consist of the noun *interaction*, the verb *interact*, or their synonyms.

In vitro **interaction** of prostaglandin F2alpha and oxytocin in placental vessels.

Cytochalasin D at 10 microM preferentially blocked the secretory effect of carbachol and its **synergism** with cAMP, whereas it had no effect on histamine- or cAMP-stimulated acid secretion within 15 min

2.3.8.5 Participant Annotation

✓Include:

- If it is specified that a particular pharmacological substance interacts with one or more other pharmacological substances, then separate events should be annotated for each pairwise combination.

Chloral hydrate and methaqualone **interact** pharmacologically with orally administered anticoagulant agents, but the effect is not clinically significant

Chloral hydrate and methaqualone **interact** pharmacologically with orally administered anticoagulant agents, but the effect is not clinically significant

2.3.9 Adverse_Effect

The *Adverse_Effect* event type should be assigned when a pharmacological substance or combination/interaction of pharmacological substances has an effect on the body that is considered to be undesirable. More specifically, the substance/combination causes a disorder to manifest itself, or to become worse.

2.3.9.1 Possible participant roles

Role	Description	Possible types
has_agent	A pharmacological substance or combination/interaction of substances responsible for the adverse effect.	Pharmacological_substance Combination DDI
affects	The disorder resulting from or worsened	Disorder

	by administration of the Agent	
has_subject	The individual or group (human or otherwise) in which the drug effect is specified to occur.	Subject
has_cue	An indication that the event is negated and/or speculated, or which provides information about the manner of the event	Negation_cue Speculation_cue Manner_cue

2.3.9.2 Attributes

Attribute Name	Description	Possible values
<i>Negated</i>	Assigned if the adverse effect is negated	
<i>Speculated</i>	Assigned if there is some degree of speculation/uncertainty specified towards the adverse effect	
<i>Manner</i>	Provides information about the rate, level or intensity of the event	High Neutral (Default) Low

2.3.9.3 Annotation scope

✓ Include:

- Explicit mentions that a substance/combination/interaction causes (or may cause) a disorder to occur

Health care practitioners should be aware of the possibility of duloxetine-induced hyponatremia, particularly in patients treated with thiazide diuretics.

This raises awareness of using multiple serotonergic narcotics and the potential precipitation of serotonin syndrome.

- Mentions that there a link (or potential link) between the use of a substance/combination/interaction and a disorder

Concurrent administration of a TNF antagonist with ORENCIA has been associated with an

increased risk of **serious infections** and no significant additional efficacy over use of the TNF antagonists alone.

Vitamin A and oral retinoids: **Concomitant administration** of vitamin A and/or other oral retinoids with acitretin must be avoided because of the **risk** of **hypervitaminosis A**

- Mentions that there no evidence of a link between a substance/combination/interaction and the occurrence of a disorder

Reproductive toxicology studies have been performed in **cynomolgus monkeys** at doses up to 5 mg/kg/week (about 62 times the human dose based on body weight) and have revealed **no** evidence of **impaired fertility** **due to AMEVIVE (Speculated)**

✗Exclude:

- DO NOT annotate Adverse_effect events if the drug causing the adverse effect is **not** mentioned.
- DO NOT annotate cases where the adverse effect clearly occurs as a result of the treatment method, rather than the drug itself.

NOTE: In the example below, it is not the ethanol itself that causes the cutaneous seeding, but rather the method of administration, i.e. as an ultrasound-guided percutaneous injection

Cutaneous seeding **after** ultrasound-guided percutaneous **ethanol** injection for treatment of hepatocellular carcinoma

- In some cases, it is unclear or ambiguous whether the adverse effect occurs as a result of the drug or the administration method; in such cases, the Adverse_effect event SHOULD be annotated

NOTE: In the example below, it is ambiguous whether the pulmonary edema was caused by the epoprostenol, or by the method of administration (i.e., infusion)

Pulmonary edema **during** acute infusion of **epoprostenol** in a patient with pulmonary hypertension and limited scleroderma.

2.3.9.4 Trigger Annotation

✓ Include:

- Triggers are usually verbs or nouns denoting causality or association

DIFFERIN Gel has the potential to produce local irritation in some patients

Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy

The clinical data suggest that anterior lumbosacral radiculopathy is also a type of neurologic complication associated with intrathecal methotrexate treatment

- Some words, such as *risk*, convey a meaning of both causality and speculation. Such words may be used as triggers if there is no other suitable trigger that conveys causality or association.
 - In such cases, the word should be annotated *both* as a trigger should and as a speculation cue for the event.

The risk of hypoglycemia secondary to this mechanism may be increased if allopurinol and chlorpropamide are given concomitantly in the presence of renal insufficiency.

- Triggers corresponding to phrasal verbs should be fully annotated

Certain drugs may lead to loss of blood glucose control.

- Fixed and/or domain-specific phrases denoting causality or association may also be annotated as triggers

In addition, reduced kidney and liver function secondary to PROLEUKIN treatment may delay elimination of concomitant medications and increase the risk of adverse events from those drugs.

- **In the absence of a trigger that explicitly denotes causality, association or risk,** other types of triggers may be chosen, when it is clear from the context that the administration of a substance/combination/interaction causes or affects a disorder
 - Triggers with a temporal meaning, such as *after* or *following*, which convey the fact that adverse effect occurred after the administration of a substance/combination/interaction

A 14-year-old female developed systemic lupus erythematosus-like symptoms two weeks after

administration of carbamazepine.

- Triggers that convey the harmful effects of the substance/combination/interaction

Our experience cautions against the further use of high-dose cytarabine in patients who develop PPE, and is a timely reminder of the potential toxicity of this agent

Marked elevation of serum CK may be a possible complication of olanzapine therapy

- In the absence of triggers such as the above, triggers such as *develop*, where it is clear from the context that the specified disorder occurred whilst taking a substance/combination

This case report describes the development of asymptomatic visual field defects (VFDs) in a psychiatric patient receiving adjunctive tiagabine treatment.

- Other verbs/nouns, in the absence of triggers of the types introduced above

Patients with HACA titers may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies

2.3.10 Potential_Therapeutic_Effect

The *Potential_Therapeutic_Effect* event type should be assigned when a pharmacological substance or combination/interaction of pharmacological substances is being administered, with the intention of having a therapeutic effect.

2.3.10.1 Possible participant roles

Role	Description	Possible types
has_agent	A pharmacological substance or combination/interaction of substances responsible for the therapeutic effect	Pharmacological_substance Combination DDI
affects	The disorder improved or cured by administration of the Agent	Disorder
has_subject	The individual or group (human or otherwise) in which the therapeutic effect	Subject

	is specified to occur.	
has_cue	An indication that the event is negated and/or speculated, or which provides information about the manner of the event	Negation_cue Speculation_cue Manner_cue

2.3.10.2 Attributes

Attribute Name	Description	Possible values
<i>Negated</i>	Assigned if the potential therapeutic effect is negated	
<i>Speculated</i>	Assigned if there is some degree of speculation/uncertainty specified towards the effect	
<i>Manner</i>	Provides information about the rate, level or intensity of the event	High Neutral (Default) Low

2.3.10.3 Annotation scope

✓ Include:

- All mentions of a pharmacological substance/combination/interaction being used for treatment. This may include:
 - Mentions of a substance/combination/interaction being administered to treat a specific disorder

Abciximab has been administered to patients with ischemic heart disease treated concomitantly with a broad range of medications used in the treatment of angina myocardial infarction and hypertension

- Mentions that a substance/combination/interaction is effective in treating a specified disorder

The **fluoroquinolones** are a rapidly growing class of antibiotics with a broad spectrum of activity **against** **gram-negative and some gram-positive aerobic bacteria**

- **If the disorder being treated is not mentioned**, then a *Potential_therapeutic_effect* event should ONLY be annotated if a suitable *Subject* phrase can be annotated as a participant of the event

Healthy subjects **received** **CLZ** to determine baseline CYP2E1 activity (CLZ plasma clearance and 6-hydroxychlorzoxazone fractional metabolic clearance)..

A **5-year-old girl** **received** 3.8 mg cumulative dose of **vincristin** before development of ptosis.

We describe serotonin syndrome after **concomitant use** of linezolid and meperidine in a **27-year-old man** with acute leukemia

- Cases where a substance/combination/interaction is stated **to have no effect on a given disorder**
NOTE: In the example below, the event trigger is also the negation cue, because it is stated that colony-stimulating factors *do not* have a therapeutic effect in this context.

Many cases are **unresponsive** to **colony-stimulating factors**

✗Exclude:

- Cases where it is stated that a treatment with a given substance/combination has been stopped, even when this course of action is stated to have a beneficial effect on a disorder

Cessation of **treatment** with **5-ASA compounds**

- Cases where it is not clear from the sentential context that a substance has been used to treat a given condition.

In the example below, there is no explicit statement that succinylcholine was specifically administered to treat any of the conditions mentioned, and so there

should not be a *Potential_therapeutic_effect* annotated in this sentence. On the other hand, there are clear *Adverse_effects* for this drug.

We believe that **mucositis** was a contributing factor to this case of **fatal hyperkalemia** after **administration** of **succinylcholine**

- Cases in which treatment with/administration of a substance/combination is mentioned, but where it is NOT possible to annotate **either** the disorder being treated **or** the subjects being treated.

NOTE: In the example below, there is mention of a combination of drugs being used for treatment. However, the specific disorder being targeted is not mentioned. Also, although the word *patients* is present, this is too general to have been annotated as a *Subject* in the entity annotation phase.

Patients **treated** with acebutolol **plus** catecholamine depletors should, therefore, be observed closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia.

2.3.10.4 Trigger annotation

✓ Include:

- Triggers will often correspond to nouns or verbs such as *treat*, *administer*, *receive* or their synonyms, as well as prepositions such as *against*

Review of these case reports indicates that the patients were mainly **receiving** **thiazide diuretics** for **hypertension** and that tests to rule out decreased renal function secondary to hypertensive nephropathy were not often performed.

18-MC, a novel iboga alkaloid congener, is being developed as a potential **treatment** for multiple forms of **drug abuse**.

- If possible, the annotated trigger phrase should denote the fact that the substance/combination/interaction is being used in a therapeutic context

Hypocalcemia after **therapeutic use** of **magnesium sulfate**.

- In cases where a sentence contains both a general word or phrase conveying the administration of a drug, and a word or phrase denoting a positive effect of the administration, the latter should be chosen as the trigger.

Clinical symptoms and leukopenia normalized after administration of prednisolone at 40 mg

3 Guideline Summaries

In this section, we provide tables that summarise the guidelines for entity, relation and event annotation; these may be used as a quick reference guide during the annotation process, after familiarity with the detailed guidelines has been established.

3.1 Entity summary table

This table provides a summary of the definitions, annotation scopes and annotation spans for each of the entity annotation categories. In most cases, such examples of spans to be annotated are provided; for examples of entity annotations in the context of complete sentences, please refer back to the detailed entity annotation guidelines provided towards the start of this document. The names of the categories are colour-coded to denote where there are sub-types of a given category.

Entity Type	Definition	Annotation Scope		Annotation Span		Examples
		Include	Exclude	Include	Exclude	
<u>Pharmacological substance</u>	<p>All pharmacological substances mentioned in text. Includes:</p> <p>Single drug or group of drugs approved for human use, referred to using either generic drug or brand name</p> <p>Active substances susceptible to interaction, but not approved for human use</p>	<ul style="list-style-type: none"> Genes/gene products used as therapeutic agents Generic drug names IUPAC and IUPAC-like chemical drug names Alcohol mentions synonymous with ethanol Endogenous substances administered as exogenous drugs. Toxins Excipients Generic or chemical names of metabolites Drugs referred to by brand name (usually starting with capital letter or all caps) Names or groups of drugs or other active substances Expressions characterising general classes of drugs 	<ul style="list-style-type: none"> Food Drink Names of alcoholic beverages Environmental chemicals Vague/non-specific references Chemical formulas of active substances Alcohol mentions referring to alkyl compounds containing a hydroxyl group. Endogenous substances not used in a therapeutic context Mentions of water and saline as excipients. Common metabolite names 	<ul style="list-style-type: none"> Drug names Separate annotations for names on either side of a hyphen Descriptive information considered part of the drug name Ions specified in salt formulations General classes of drugs denoting groups Words denoting groups of drugs, e.g., <i>agents</i>, <i>drugs</i>, <i>agonists</i> Words following anatomical entities/disorders denoting drug used in their treatment, e.g. <i>products</i> Adjectives needed to fully characterise group, e.g. <i>atypical</i> 	<ul style="list-style-type: none"> Words indicating the effects of drugs Dosage Administration route References to therapy using the drug Generic words referring to salts 	<ul style="list-style-type: none"> <i>didanosone</i> <i>5-hydroxy-L-tryptophan</i> <i>MPTP</i> <i>Tween80</i> <i>Threohydrobupropion</i> <i>oxycodone</i> <i>hydrochloride</i> <i>Plenaxis</i> <i>DIAMOX</i> <i>fluoroquinolones</i> <i>anticoagulant</i> <i>homodimeric disintegrin</i> <i>dopamine D1 receptor antagonist</i> <i>neurotoxin</i>

Entity Type	Definition	Annotation Scope		Annotation Span		Examples
		Include	Exclude	Include	Exclude	
<u>Subject</u>	An organism, cell line, bacterium or group thereof, whose characteristics are under discussion. The organism may be human or otherwise	<ul style="list-style-type: none"> General references to groups of subjects or specific classes of subjects according to characteristics Names of specific species under discussion Names of bacteria under discussion Expressions that specify a number of subgroup of subjects 	<ul style="list-style-type: none"> Vague references to subjects that do not refer to characteristics (e.g., <i>patients</i>) unless: <ul style="list-style-type: none"> accompanied by number or subgroup information when information about disorders suffered by the subjects(s) are mentioned in close proximity, to further characterise the patients 	<ul style="list-style-type: none"> Subject characteristics (e.g., sex, age, race) Adjectives denoting subjects with no disorder. References to number of subjects References to a subset of subjects 	<ul style="list-style-type: none"> Adjectives referring to disorders that characterise the subjects 	<ul style="list-style-type: none"> <i>children</i> <i>mice</i> <i>male Wislar rats</i> <i>73-year-old African American man</i> <i>hypertensive subjects</i> <i>normotensive subjects</i> <i>some patients</i> <i>21 normal females</i> <i>3 of the 21 subjects</i>
<u>Disorder</u>	An observation about a medical subject's body or mind considered to be abnormal or caused by a disease, pharmacological substance or DDI.	<ul style="list-style-type: none"> Medical conditions Mental or behavioural dysfunction Abnormalities in physiological functions Neoplastic processes Pathological processes 	<ul style="list-style-type: none"> Changes to clinical attributes, measurements or anatomical entities that are described using verbs 	<ul style="list-style-type: none"> Anatomical locations forming part of disorder name Modifiers with a special meaning, considered part of the condition name, e.g., 	<ul style="list-style-type: none"> Modifiers referring to the severity of the disorder that are not considered part of the condition name Modifiers corresponding to the cause or 	<ul style="list-style-type: none"> <i>urinary tract infection</i> <i>stereotyped behaviour</i> <i>drug abuse</i> <i>hyperlocomotion</i> <i>peritoneal metastasis</i> <i>cerebellar</i>

		<ul style="list-style-type: none"> • Damage to anatomical entity caused by disease or drugs • Signs or symptoms caused by a medical condition/disease, drug or DDI • Sets of signs or symptoms (e.g., syndromes) • Abnormalities in clinical attributes or measurements as noun phrases • Injuries or toxicities 		<p><i>chronic</i></p> <ul style="list-style-type: none"> • Modifiers of the noun “effects” (or a synonym) that refer to a disorder. • Disorders specified as adjectives 	<p>origin of the disorder</p> <ul style="list-style-type: none"> • General expressions not referring to specific disorder • The word “effects” (or a synonym), when disorder is a modifier of this word. 	<p><i>damabge</i></p> <ul style="list-style-type: none"> • <i>whole body tremors</i> • <i>Serotonin syndrome</i> • <i>concentrated urine</i> • <i>schizophrenic</i> • <i>Bacillus subtilis</i> • <i>clinical toxicities</i> • <i>changes in blood pressure</i>
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3.2 Relation summary table

Relation	Definition	Entity 1	Entity 2	Annotation Scope	Example
<u>is_equivalent</u>	Links an entity with an alternative name or form, e.g. <ul style="list-style-type: none"> A full entity name and its short form or acronym A generic drug name and an associated brand name 	Any	Any (but sharing the same category as Entity 1)	<ul style="list-style-type: none"> Link alternative forms/names of the same entity that are mentioned within the same sentence Do not link duplicate mentions of the same form of an entity appearing in the same sentence 	<p>As immediate-early genes (IEGs) are thought to play a critical role in mediating stimulus-induced neural plasticity</p> <p>Intravenous Adenocard (adenosine) has been effectively administered in the presence of other cardioactive drugs</p>
<u>Subject_Disorder</u>	Links a <i>Subject</i> to <i>Disorder</i> used to characterise the subject(s)	Subject	Disorder	<ul style="list-style-type: none"> Link disorder that specifically characterises a subject. Typically: <ul style="list-style-type: none"> Disorder occurs close to <i>Subject</i> often following a phrase such as <i>with</i> Disorder may be expressed as adjective 	<p>Lupus-like syndrome caused by 5-aminosalicylic acid in patients with inflammatory bowel disease.</p> <p>Case 1 was a schizophrenic male with a history of NMS under treatment with aripiprazole 20 mg</p>
<u>Coreference</u>	Links event participants, that are too general to be annotated as entities, to the specific entities that the event participants refers to.	Coreferring mention – Previously un-annotated, general event argument	Any – Any entity referred to by the more general event participant phrase	<ul style="list-style-type: none"> Event participant is a general phrase not previously annotated as an NE. Clear references to more specific instances of annotated in neighbouring sentence 	<p>Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides.</p>

3.3 Event summary tables

The tables in this section (one per event) provide summaries of the guidelines for each individual event type. Each table includes general definitions, summaries of the possible roles and attributes, and overviews of annotation scopes, trigger and participant annotation guidelines. A small number of examples for each event type is also provided

3.3.1 Combination

Type	Definition	Possible Roles			Attributes		
<u>Combination</u>	A specification that two or more pharmacological substances are being used at the same time	Name	Description	Possible Types	Name	Description	Possible Values
		has_ participant	Substance involved in the interaction	Pharmacological _substance	<i>Negated</i>	Assigned if the event is negated	
		has_cue	An indication that the event is negated	Negation_cue Speculation_cue Manner_cue	<i>Speculated</i>	Assigned if the combination is speculated	
					<i>Manner</i>	Provides information about the rate, level or intensity of the event	High Neutral (Default) Low
Annotation Scope		Trigger Annotation			Participant Annotation		
Include	Exclude	Include	Exclude	Include	Exclude		
<ul style="list-style-type: none">All mentions of combinations, regardless of whether there are any effects	<ul style="list-style-type: none">Explicit mention of interactions between substances	<ul style="list-style-type: none">Should denote meaning similar to <i>combination</i> or <i>taken /administered in combination</i>Annotate fixed phrases with the above meaning, e.g., <i>in the presence of</i>Include words denoting intake or administration in the trigger span		<ul style="list-style-type: none">Annotate separate events for each specified pairwise combination of substances			
<ul style="list-style-type: none">Catecholamine-depleting drugs, such as reserpine, may have an additive effect when given with beta-blocking agentsThe AUC values of nifedipine in the presence of cimetidine were between 1.52 and 2.01 times those in the absence of cimetidine.							

3.3.2 DDI

Type	Definition	Possible Roles			Attributes		
DDI	A specific mention that there is an interaction between two or more pharmacological substances	Name	Description	Possible Types	Name	Description	Possible Values
		has_participant	Substance involved in the interaction	Pharmacological_substance	Negated	Assigned if the interaction is negated	
		has_cue	An indication that the interaction is negated and/or speculated, or about the manner of the event	Negation_cue Speculation_cue Manner_cue	Speculated	Assigned if the interaction is speculated	
					Manner	Provides information about the rate, level or intensity of the event	High Neutral Low
Annotation Scope		Trigger Annotation			Participant Annotation		
Include		Exclude	Include	Exclude	Include		Exclude
<ul style="list-style-type: none">Explicit mentions of interactions between two or more pharmacological substances.Explicit mentions that an interaction does not occur between two or more pharmacological substances, or that the interaction is uncertain		<ul style="list-style-type: none">Mentions of combinations of pharmacological substances that do not explicitly mention an interaction.	<ul style="list-style-type: none">Normally the noun <i>interaction</i>, the verb <i>interact</i>, or a synonym		<ul style="list-style-type: none">Separate events should be annotated for each specified pairwise combination of interacting substances		<ul style="list-style-type: none">
<ul style="list-style-type: none">There is little if any clinically significant interaction between Acarbose and metformin.Cytochalasin D at 10 microM preferentially blocked the secretory effect of carbachol and its synergism with cAMPIn vitro interaction of prostaglandin F2alpha and oxytocin in placental vessels							

3.3.3 Adverse_effect

Type	Definition	Possible Roles			Attributes			
Adverse effect	Agent causes a disorder to manifest itself, or to become worse.	Name	Description	Possible Types	Name	Description	Possible Values	
		has_agent	Entity/event responsible for the adverse effect	Pharmacological_substance Combination DDI	Negated	Assigned if the Effect is negated		
		affects	The disorder resulting from or worsened by Agent	Disorder	Speculated	Assigned if the effect is speculated		
		has_subject	Individual or group in which adverse effect occurs	Subject	Manner	Provides information about the rate, level, intensity of the event	High Neutral Low	
		has_cue	Indication event is negated/speculated, or manner information	Negation_cue Speculation_cue Manner_cue				
Annotation Scope			Trigger Annotation		Participant Annotation			
Include		Exclude	Include		Exclude	Include		Exclude
<ul style="list-style-type: none">Agent causes disorder to occurLink between use of Agent and disorderMentions that there is no link or lack of evidence for link between Agent and occurrence of disorder		<ul style="list-style-type: none">Events where no drug or combination is mentioned	<ul style="list-style-type: none">Verbs or nouns that denoting causality, associationPhrasal verbs with above meaningFixed or domain-specific phrases with one of the above meanings (e.g. <i>secondary to</i>) In absence of causality/association trigger, trigger may denote risk, have temporal meaning or convey a harmful effect					
<ul style="list-style-type: none">Concomitant administration of vitamin A and/or other oral retinoids with acitretin must be avoided because of the risk of hypervitaminosis AReproductive toxicology studies have been performed in cynomolgus monkeys and have revealed no evidence of impaired fertility due to AMEVIVEA 14-year-old female developed systemic lupus erythematosus-like symptoms two weeks after administration of carbamazepineOur experience cautions against the further use of high-dose cytarabine in patients who develop PPE, and is a timely reminder of the potential toxicity of this agentMarked elevation of serum CK may be a possible complication of olanzapine therapy								

3.3.4 Potential therapeutic_effect

Type	Definition	Possible Roles			Attributes		
Potential therapeutic effect	A pharmacological substance or combination/interaction of pharmacological substances is being used as a treatment, possibly with a therapeutic effect on a mentioned disorder.	Name	Description	Possible Types	Name	Description	Possible Values
		has_agent	Entity/event responsible for the therapeutic effect	Pharmacological_substance Combination DDI	Negated	Assigned if the effect is negated	
		affects	Disorder improved/cured by Agent	Disorder	Speculated	Assigned if the effect is speculated	
		has_subject	Individual or group in which the therapeutic effect occurs	Subject	Manner	Provides information about the rate, level or intensity of the event	High Neutral Low
		has_cue	Indication that event is negated/speculated, or manner inform	Negation_cue Speculation_cue Manner_cue			
Annotation Scope			Trigger Annotation		Participant Annotation		
Include	Exclude	Include	Exclude	Include	Exclude		
<ul style="list-style-type: none">Agent is administered to treat specific disorderAgent is effective in treating disorderAgent is used for treatment, even when disorder not mentionedAgent stated to have no effect on disorder	<ul style="list-style-type: none">Treatment with agent has been stopped, even if this improves disorder	<ul style="list-style-type: none">Nouns or verbs such as <i>treat</i>, <i>administer</i>, <i>receive</i> and synonymsPrepositions such as <i>against</i>Words denoting that therapeutic use of agentWords denoting positive effect of agent when present					
<ul style="list-style-type: none">Abciximab has been administered to patients with ischemic heart diseaseThe fluoroquinolones are a rapidly growing class of antibiotics with a broad spectrum of activity against gram-negative and some gram-positive aerobic bacteriaPatients treated with acebutolol plus catecholamine depletors should, therefore, be observed closely for evidence of bradycardia or hypotensionClinical symptoms and leukopenia normalized after administration of prednisolone at 40 mgMany cases are unresponsive to colony-stimulating factors							