Annotation Guidelines
TAC 2017 Adverse Drug Reaction Extraction from Drug Labels

The following guidelines are presented to participants to help understand why certain annotation choices were made, based on issues brought up during the annotation process. The overview of the task and annotations should be read first, as it provides a complete high-level overview of the annotations. For the most part, the examples below represent the hard, corner cases for adverse drug reaction annotation based on questions and disagreements among the annotators. It is not intended to be a complete documentation of every reason to annotate, or not annotate, a given mention, relation, or reaction.

Furthermore, due to the specific needs of FDA, there are some atypical choices made in terms of what and how certain annotations are created. This document is not intended to provide a complete justification for these reasons, simply the specific annotation decisions.

Definitions

FDA guidelines define adverse events, adverse reactions and severe adverse reactions as shown here:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf

Adverse Event: "refers to any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related."

Adverse Reaction: "an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and ECG."

Serious Adverse Reaction: "refers to any reaction occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect."

Fine-Grained Linguistic Annotation (Tasks 1 and 2)

Annotate Adverse Events, Adverse Reactions, and Serious Adverse Reactions (defined above) as **AdverseReaction (AR)** mentions. The semantic types of the mentions to be annotated are in the UMLS semantic group Disorders.

Annotate all occurrences of an **AdverseReaction** in the text, even if AR is a broad class of disorders. Annotate all adverse reactions in the following sentence, including eye disorders:

(1) *Most commonly observed adverse reactions (> 5% of patients) are: muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, neck pain, musculoskeletal pain, dysphonia, injection site pain, and eye disorders*.

Annotate AR instances only once in the following order asserted > hypothetical > negated. For example, if only "*TNF blockers*" in Example (2) below were mentioned, we would have annotated "*ANA*" [Antinuclear Antibodies] as hypothetical due to class effect (see below), but the sentence also indicates that the **AR** was reported for the label drug CIMZIA, so annotate this **AR** as asserted.

(2)   *In clinical trials of TNF blockers, including CIMZIA, in patients with RA, some patients have developed* **ANA**.

Annotate all **AR**s in "chains of events", i.e. Clinical Outcomes of AR (long-term sequelae). Do not establish causal relations in the chains: annotate each AR separately, for example, annotate "*Rhabdomyolysis*" and "*acute prerenal failure*" separately in:

(3)   **Rhabdomyolysis** *resulting in* **acute prerenal failure** *and long-term dialysis has been associated with Livalo.*

Note: If a more specific **AR** could be inferred from the sequence of events, add an inferred annotation. For example, in "*Sepsis followed by shock*", annotate sepsis alone, shock alone, and sepsis + shock.

Mentions in the UMLS semantic group Disorders play semantic roles other than AdverseReactions. **Annotate** only **AdverseReaction**s and **do not** annotate mentions in the following semantic roles: Contraindications, Indications, Conditions associated with indications, and Risk factors or predisposing conditions for experiencing AR. Additionally, do not annotate withdrawal symptoms: these are not ARs caused by the drug.

Do not annotate immunoreactivity and antibodies within normal limits or any other normal physiologic processes. **Annotate** abnormal immunogenicity, e.g., annotate "*ANA*" in Example (2).

Do not annotate monitoring for **AR** or tests to diagnose an **AR**, for example, do not annotate hypertension, hypokalemia, and fluid retention in "*Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month*." Similarly, do not annotate anything in the following:

(4)   *BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of BYDUREON and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for detection of MTC in patients treated with BYDUREON [see Contraindications (4.1) and Warnings and Precautions (5.1)].*

Do not annotate therapeutic recommendations. For example, do not annotate pancreatitis in "*TANZEUM has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.*"

Do not annotate general background information. For example, do not annotate "*overgrowth of C. difficile*" in "*Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of C. difficile*"

Do not annotate general lab test results. For example, do not annotate "*hematology laboratory test*" in "*The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2.*"

Do not annotate **AR**s of a non-label drug of a different class that was used concomitantly with the label drug. For example, do not annotate TEN in the following:

(5)   *In a study of TREANDA (90 mg/m 2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert).*

Do not annotate section headings: while many headers could be easily mapped to MedDRA PTs, these are often general and do not adequately describe the specific **AR** that the label is attempting to convey. For example, only the following should be annotated in Examples (6)-(8):

(6)   *Nervous System Disorders –* *Headache*
(7)   *Gastrointestinal Disorders –* *Nausea, Diarrhea*
(8)   *Reproductive System and Breast Disorders –* *Gynecomastia, Breast Enlargement*

Do not annotate general subheadings in the lists, e.g. Example (2), and tables, e.g. Example (3) below. Do not annotate *Skin and subcutaneous tissue disorders*; **annotate** the specific skin disorders (highlighted).   Do not annotate *Infections and infestations* and *Respiratory disorders* even if occurrence data are provided and more specific disorders are not listed or the counts for more specific disorders don't add up to the general subheading total.

(9)

Skin and subcutaneous tissue disorders	57
Rash	27
Pruritis	17
Alopecia	13
Infections and infestations	13
Respiratory disorders	12
Dysphonya	6

Note: Annotate bulleted lists if they are clearly introduced as lists of adverse reactions, e.g., "*The following adverse reactions are described in greater detail in other sections:*" If a list item consists of a heading and an enumeration of **AR**s, **do not** annotate the heading. For example, do not annotate "*Bullous and Exfoliative Skin Disorders*" in the first bullet of Example (10) below. **Exception:** if only the header mentions the **AR** and it is clear that it was omitted from the enumeration/incidence description, annotate the header, e.g., annotate "*ILD*" and "*keratitis*" as shown in Example (10).

(10)
- *Bullous and Exfoliative Skin Disorders:* *Severe bullous*, *blistering,* and *exfoliating lesions occurred in 0.15% of patients. Discontinue for life-threatening cutaneous reactions. Withhold GILOTRIF for severe and prolonged cutaneous reactions. (2.3, 5.2)*
- *Interstitial lung disease (ILD): Occurs in 1.5% of patients. Withhold GILOTRIF for acute onset or worsening of pulmonary symptoms. Discontinue GILOTRIF if ILD is diagnosed. (2.3, 5.3)*
- *Hepatic toxicity:* *Fatal hepatic impairment occurs in 0.18% of patients. Monitor with periodic liver testing. Withhold or discontinue GILOTRIF for severe or worsening liver tests. (2.3, 5.4)*
- *Keratitis: Occurs in 0.8% of patients. Withhold GILOTRIF for keratitis evaluation. Withhold or discontinue GILOTRIF for confirmed ulcerative keratitis. (2.3, 5.5)*

The descriptions of **AdverseReaction** might require the following details to be annotated in the form of mentions (**purple**) and relations (**orange**).

➔ **Negation** and **Negated**

AdverseReactions can be negated in the text. **Annotate** the negation triggers for negated events and the **Negated** relation: in "*There were* *no infusion-related reactions* *reported*".

Annotate ARs in the placebo arms as negated events. Annotate the **AdverseReaction**, the "*placebo*" as **Factor** and connect with the **Negated** relation. For instance:

(11) *Mycotic infections occurred in 0.5% of patients treated with placebo*.

- **Animal**/**DrugClass**/**Factor** and **Hypothetical**

FDA guidelines indicate that "there are circumstances in which an adverse reaction that has not been observed with a drug can nonetheless be anticipated to occur." The events are anticipated (referred to here as hypothetical) if they were observed in <u>animal trials</u> or in other drugs of the <u>same drug class</u>. Annotate the evidence for the hypothesis (**Animal**, **DrugClass** or other **Factor**) and the **Hypothetical** relation. For instance, the DrugClass "*IL-1 inhibitorts*" should be connected to both **AdverseReaction**s via a **Hypothetical** relation in the following:

(12) *Use of IL-1 inhibitors increases reactivation of tuberculosis or opportunistic infections*

Annotate hedging as **Hypothetical**, labeling modality markers (e.g., should, might, may, could) as **Factor**. For example, the **Factor** "*may*" should be connected to "*paradoxical bronchospasm*" via a **Hypothetical** relation:

(13) *TUDORZA PRESSAIR may cause paradoxical bronchospasm*

- **Severity** and **Effect**/**Negated**

Annotate the **Severity** of the **AdverseReaction** and connect via an **Effect** relation (unless the severity indicates a **Negated** relation, e.g., "normal levels"). For instance, in the following "*Grade 1-3*" is a **Severity**, connected via an **Effect** relation to "*palmar-plantar erythrodysesthesia syndrome*":

(14) *Grade 3 palmar-plantar erythrodysesthesia syndrome*

If an **AR** contains ranges, for example, "*Grade 1-3*" as opposed to the single grade shown in Example (14), **Annotate** the ends of the range as disconnected spans (not shown above due to difficulty conveying in a text document). But given "*Grade 1-3*", then three **Severity** annotations would be created: (i) "*Grade 1-3*", (ii) "*Grade 1*", and (iii) "*Grade*" and "*3*" as a disconnected span (possible in Brat). All three would then be connected to the **AdverseReaction** using an **Effect** relation. Annotate only clearly stated grades; **do not** annotate unknown grades, e.g., "*grade greater than 3*" should not be annotated. If **Severity** does not pertain to all patients annotate the **AR** twice – once with **Severity** and once without, for example, in the following "keratits" should be annotated twice, and only once connected (via **Effect**) with the **Severity** "*Grade 3*":

(15) *keratitis was reported in 5 patients, with Grade 3 in 1*.

Note: Annotate "*fatal*" as **AdverseReaction**, not **Severity**.

Note: Limit all relation annotations to one sentence.

EXAMPLE PARTIAL DOCUMENT: VIBATIV (BOXED WARNING)

> - Patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased **mortality** observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk. (5.1)
> - Nephrotoxicity: **New onset** or **worsening renal impairment** has occurred. Monitor renal function in all patients. (5.3)
> - Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. (5.4, 8.1)
> - Avoid use of VIBATIV during pregnancy unless potential benefit to the patient outweighs potential risk to the fetus. (8.1)
> - **Adverse developmental outcomes** observed in 3 **animal** species at clinically relevant doses raise concerns about **potential adverse developmental outcomes** in humans. (8.1)

Note the following annotations (or lack thereof):

- *renal impairment*: this text in the first sentence would <u>not</u> be annotated because it is a pre-existing condition.
- *CrCl ≤50 mL/min*: would <u>not</u> be annotated because it is a pre-existing condition.
- *hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia*: this would <u>not</u> be annotated because these are indications.
- *mortality:* this would be annotated because this is an **AR**.
- *nephrotoxicity:* this would <u>not</u> be annotated because it is a header.
- *new onset renal impairment:* This disconnected span is an **AR**.
- *worsening renal impairment*: This is an **AR**.
- *monitor renal function*: this would <u>not</u> be annotated because it is a monitoring recommendation.
- *pregnancy test*: this would <u>not</u> be annotated because it is a therapeutic recommendation/diagnostic work-up.
- *pregnancy*: this would <u>not</u> be annotated because it is a contraindication/therapeutic recommendation (avoid use during pregnancy).
- *adverse developmental outcomes* (first instance): this would be annotated because it is an **AR** and would also be connected to *animal* (type **Animal**) using a **Hypothetical** relation.
- *adverse developmental outcomes* (second instance): this would be annotated because it is an AR and would also be connected to *potential* (type **Factor**) using a **Hypothetical** relation.

Drug Label Reference Standard (Tasks 3 and 4)

For each drug label, the reference standard consists of a set of distinct **AdverseReaction**s mapped to MedDRA preferred term (PT). Note that it is additionally possible for an **AR** to (i) have no mapping to MedDRA, (ii) map to a higher level term, or (iii) map to multiple PTs. When the MedDRA lower level term (LLT) better matches an **AR**, the LLT will be provided in addition to its corresponding PT.

The following process will be used to map each **AdverseReaction** to the relevant PT(s):

1) Use the UTS API to automatically obtain candidate CUIs for each **AdverseReaction** that is **asserted** in the label (an *asserted* **AdverseReaction** has no **Negated** relation, nor a **Hypothetical** relation with an **Animal** or **DrugClass**). Only retain those CUIs for which the **AdverseReaction** string exactly matches the UMLS term.

   2) If one **AR** term maps to several CUIs, manually pick one most appropriate CUI.

   3) Manually search the UTS browser for **AdverseReaction**s that did not have an exact CUI match. If no semantically equivalent term can be found, mark the **AR** as CUI-less and try to find a PT directly, using https://tools.meddra.ord/wbb/

4) Use the LHC CUI-to-MedDRA PT converter to obtain preferred terms for each CUI

5) Manually verify that the **AdverseReaction** term and PT match. If the term and PT match exactly or semantically (for example "*cardiac failure*" in text = "*heart failure*" in PT) you are done.

   6) If the PT doesn't match the **AR** semantically, do a manual search using https://tools.meddra.org/wbb/.

   7) If one CUI maps to several PTs, pick the PT that is closest to the AR term in the text.

   8) In no CUI-to-PT match was found, manually search https://tools.meddra.org/wbb/ If a term semantically equivalent to the AR cannot be found, mark the AR as PT-less

9) Review all PT-less terms in a meeting with all annotators.