Guidelines for Drug-Disease-Symptom annotation in Twitter and PubMed texts.
Introduction
The goal of this project is to create an annotated corpus of symptoms, diseases, and drugs mentions in sentences taken from PubMed articles and from tweets. In the rest of the document we will refer to the symptoms, diseases, and drugs using their capitalized form (SYMPTOMS, DISEASES, and DRUGS) when we talk about the generic entities that are to be annotated. For this study we focus on a closed set of DRUGS (Table A1, in the appendix), although the study is not limited to them, and any mention of any DRUG in our closed list of DRUGS should be annotated.

This document provides a definition of SYMPTOM, DRUG, and DISEASE, the relations between these entities, and the guidelines to be followed during the annotation. In case there is some question not covered in this document, please send an e-mail to: nestoralvaro@nii.ac.jp.

In these guidelines we describe each one of the 3 types of entities (DRUGS, SYMPTOMS, and DISEASES), the attributes of the entities, and the 3 types of relations (reason to use, outcome-positive, outcome-negative) that are to be annotated.

Annotation of entities
An entity can be a single word such as “tiredness” as it appears in the sentence “the patient was experiencing tiredness”, or a span of text such as “could not move from the couch” obtained from the sentence “I worked out so hard that when I got back home I could not move from the couch”. Both entities refer to the concept “tiredness symptom” (MEDDRA Code 10043890).

We provide a list of entities, the definition of each one and an example in Table 1. The only DRUGS to be annotated are those appearing in Table A1. In the following examples DRUGS are highlighted in green, SYMPTOMS in blue, and DISEASES in red.

| Entity   | Definition                                                                 | Example                                      |
|----------|---------------------------------------------------------------------------|----------------------------------------------|
| DRUG     | Any of the marketed medicines that appears in the SIDER database          | The prescription included Lexapro.           |
|          | (http://sideeffects.embl.de/), which is also listed in our closed set of   |                                               |
|          | drugs (See Table A1).                                                    |                                               |
| SYMPTOMS | Any sign or SYMPTOM contained within the MedDRA ontology                  | Adderall kept me focused.                    |
|          | (http://bioportal.bioontology.org/ontoologies/MEDDRA).                    |                                               |
| DISEASE  | Any DISEASE contained within the MedDRA ontology.                         | The patient suffered from sleep deprivation  |
|          | (http://bioportal.bioontology.org/ontoologies/MEDDRA).                    | without trazodone.                           |

Table 1: Entities to be annotated.

Annotation of attributes
The entities (DRUGS, SYMPTOMS and DISEASES) have some attributes that will be annotated to
We provide a list of attributes for the entities, the definition of each one, the values each attribute can take, and an example in Table 2. Some attributes have **default values (in bold and highlighted in the table)** which will be used when no attribute is chosen.

In the following examples **DRUGS** are highlighted in green, **SYMPTOMS** in blue, and **DISEASES** in red.

| Attribute | Definition | Values | Examples |
|-----------|------------|--------|----------|
| **Polarity** | Indicates whether the entity is negated or not. The negation has to be a linguistic negation (“not”, “don’t”...). | • **Positive**: The entity is not negated. Default value. • **Negative**: The mention of the entity is negated. | “I took **prozac** and now I don’t have a **headache**”  
**Prozac**: polarity=positive (left blank)  
**Headache**: polarity=negative |
| **Person** | Indicates whether the entity is affecting the “1st”, “2nd”, “3rd” person, or whether there is no information. This attribute is based on the original sender. | • **1st**: The entity is described from a “first person” point of view. The entity is directly impacting the author of the text. Relates a first hand experience. • **2nd**: The entity is described from a “second person” point of view. The entity is impacting another person whom the author knows. • **3rd**: The entity is described from a “third person” point of view. The entity is impacting someone not directly related with the author of the text. • **Not available**: There is no clear reference to whom the entity is impacting. Default value. | “I took **prozac** and now I don’t have a **headache**”  
**Prozac**: Person=1st  
The entity is described in first person.  
**Headache**: Person=1st  
“**Hate** **prozac**”  
**Prozac**: Person=not available (value left blank). |
| **Modality** | Indicates whether the entity is stated in an “actual”, “hedged”, “hypothetical” or “generic” way. | • **Actual**: These mentions have already happened or are being scheduled (without hedging) to happen. Default value. • **Hedged**: These mentions include lexical (“seems”, “likely”, "suspicious", "possible", "consistent with”), or phrasal (“I suspect that...", "It would seem likely that") hedging. These entities are strongly implied, but, for safety, liability, or due to lack of comprehensive evidence, are not stated as a fact. • **Hypothetical**: Will often follow "if" statements ("If X happens, then we’ll use Y to treat Z") or other sorts of conditionals ("Depending on the patient’s response, we might treat A | “**The patient did not report nausea**”  
**Nausea**: Modality=Actual  
“**The patient may have undergone a mild stroke**”  
**Stroke**: Modality=hedged  
“We suspect either **achalasia** or **pseudoachalasia** here”  
**Achalasia**: Modality=Hypothetical  
**Pseudoachalasia**: Modality=Hypothetical  
“**Adderall** should not be taken” |
| **Exemplification** | Indicates whether the entity is presented using an example or a description. Only to be used when the entity is presented through an exemplification. |
|---------------------|-------------------------------------------------------------------------------------------------|
| ● **Positive:** When an exemplification is used to present the entity. | “I will not be able to get up unless I take my Adderall”  
I will not be able to get up: Exemplification=True Indicates “lack of energy” (SNOMED ID: 248274002)  
Adderall: Exemplification=Negative (value left blank). |
| ● **Negative:** The entity is not presented through an example. Default value. | |

| **Duration** | Indicates whether the entity’s lasting span is “Intermittent”, “Regular”, “Irregular”. If the duration is not indicated the attribute is left empty. In the case of DRUGS this attribute refers to the time span when the DRUG has been taken. |
|-------------|-------------------------------------------------------------------------------------------------|
| ● **Regular:** The entity has a continued lasting span. | “I had a strong headache last night, so I took prozac.”  
Prozac: Duration=not available (the value will be left empty)  
Headache: Duration= ”Irregular” |
| ● **Intermittent:** The lasting span of the entity has been recurring. | “I have been on Prozac for 5 years now”  
Prozac: Duration= ”Regular” |
| ● **Irregular:** There is indicated that there is no pattern in the lasting span of the entity. | |
| ● **Not available:** When the duration is not indicated. Default value. | |

| **Severity** | Indicates whether the seriousness of an entity is “Mild”, or “Severe”. If the severity is not indicated the attribute is left empty. This attribute does not apply to DRUGS. |
|--------------|-------------------------------------------------------------------------------------------------|
| ● **Mild:** There is gentle (not acute, nor serious) severity of the entity. | “I had a strong headache last night, so I took prozac.”  
Prozac: Severity=not available (the value will be left empty)  
Headache: Severity= ”Severe” |
| ● **Severe:** There is a grave or critical seriousness of the entity. | |
| ● **Not available:** When the severity of the entity is not indicated. Default value. | |

| **Status** | Indicates whether the duration of the entity is “Complete”, or “Continuing”. If the duration is not indicated the attribute is left empty. In the case of | |
|------------|-------------------------------------------------------------------------------------------------|
| ● **Complete:** If the entity is already not showing evidence of its effects. | “I had a strong headache last night, so I took prozac.”  
Prozac: Status=not available (the value will be left empty)  
Headache: Status= ”Completed” |
| ● **Continuing:** If the entity is still showing evidence of its effects. | |
| ● **Not available:** When the status is not indicated. Default value. | “I took prozac 2 hours ago, but |
DRUGS this attribute refers to the time span when the DRUG is perceived as having effect.

**Sentiment**
- **Positive**: The entity is referenced as something good.
- **Negative**: The entity is referenced as something bad.
- **Neutral**: There is no clear point of view towards the referenced entity. Default value

“I had a strong headache last night, so I took prozac.”

**Prozac**: Sentiment=neutral (the value will be left empty)

**Headache**: Sentiment=”Negative”

**Entity identifier**
- **XXXXXXX**: The concept identifier.
  - The database contains a set of concepts obtained as follows:
    - For SYMPTOMS and DISEASES the concept identifiers represent the **UMLS concept ID** for the MedDRA term.
    - For DRUGS the concept identifiers represent the **PubChem concept ID** referenced in SIDER database for that concept.
- **-1**: If there is no concept identifier for an entity this value will be “-1”. This value can not be used for drugs (if the drug is not in the list it should NOT be annotated)

“I had a strong headache last night, so I took prozac.”

**Prozac**: ID=“3386”

**Headache**: ID=“10019211”

| Relation | Definition | Example |
|----------|------------|---------|
| Reason to use | Represents the relation appearing when a SYMPTOM or DISEASE leads to the use of some DRUG. | **Prozac** is indicated for patients with major **depressive disorder**. |
| Outcome-positive | Represents the relation between a DRUG, and an expected or unexpected SYMPTOM or DISEASE appearing after the DRUG consumption. The outcome has to be positive. | I wish I was prescribed adderall, I'd lose weight. |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Outcome-negative | Represents the relation between a DRUG, and an expected or unexpected SYMPTOM or DISEASE appearing after the DRUG consumption. The outcome has to be negative. | The most common adverse events reported for fluoxetine were impulsivity and poor concentration. |

Table 3: Relations to be annotated.

It is important to notice that the annotation tool validates the origin-entity and the end-entity of each relation. This means that:

- “Reason to use” relation: Has to start on a “SYMPTOM” or a “DISEASE” and be directed towards a “DRUG”.
- “Outcome-positive” relation: Has to start on a “DRUG”, and be directed towards a “SYMPTOM” or “DISEASE”.
- “Outcome-negative” relation: Has to start on a “DRUG”, and be directed towards a “SYMPTOM” or “DISEASE”.


Practical issues

In the following examples DRUGS are highlighted in green, SYMPTOMS in blue, and DISEASES in red.

What to annotate?

Entities

- Each mention of an entity should be annotated exactly once. Each annotation should refer to exactly one mention of the entity. All the entities should be annotated each time they are mentioned.
- Annotate mentions with morphological variations such as adjectives.
  - For instance, “hypertensive” is annotated as “hypertension.”.
  - Hashtags, whenever present, will be included in the annotation span.
  - In the sentence “I had a terrible #headache” the concept to be annotated is #headache (including the hashtag).
- Synonyms or descriptions for SYMPTOMS and DISEASES should be annotated.
  - Example: “I Took Adderall and now I’m gonna be up for hours”
    - “up for hours” should be annotated as a synonym of “Sleeplessness” (notation “10041017” in MEDDRA)
- The annotations should only include the entity mention, keeping it as specific as possible, and annotate the most specific entity mentions and select the best-matching Concept ID from SIDER database (for DRUGS) or MedDRA ontology (for SYMPTOMS and DISEASES).
  - For instance, the complete phrase “partial seizures” (ID: 10061334) should be preferred over “seizures” (ID: 10039910) as it is more specific.
  - If present, the mention span should include terms such as disease, syndrome, disorder, infection.
- Mentions of cancer, tumour, neoplasm, or infection, and other generic mentions to DISEASES/SYMPTOMS additional information, can be annotated, although it may happen that the identifier for that concept is not contained in the list of concepts.
  - In this case the ID for the concept would be “-1”
- An entity could be an acronym.
  - A long form, short form pair should be annotated as two mentions. Example: "Attention deficit hyperactivity disorder (ADHD)". In this case “Attention deficit hyperactivity disorder” and “ADHD” should be annotated separately.
- This study is focused in a closed set of DRUGS (Table A1).
  - That list of DRUGS also includes the brand names for these DRUGS.
    - Any mention of any of this DRUGS (including the brand names) has to be always annotated.
    - Those drugs have different brand names and trade names. These variants have to be annotated too.
  - For example, the table contains “Adderall”, but “Adderall XR” and it should be annotated (using the DRUG identifier for "Adderall", 3007)
- Lists and co-ordinations are phrases which mention multiple entities in a complex way. A simple illustrative example is “breast and ovarian cancer”, which refers to the entities “breast cancer” and “ovarian cancer”.
  - These constructs often overlap or do not explicitly mention some terms.
  - As the tool allows discontinuous annotations each entity should be annotated one time. One annotation would be “breast cancer” and the second annotation would be “ovarian cancer”.
- A retweet is a re-posting of someone else’s Tweet. In this case the tweet will be considered
as if the user re-posting it would be author of the tweet. Retweets are indicated by the string “RT” at the beginning of the message.

- Example: “RT I took prozac and now I don’t have a headache”
  - This example is a retweet of “I took prozac and now I don’t have a headache”, so it would be annotated as if it were “I took prozac and now I don’t have a headache”
    - Prozac: Person=1st
      - The entity is described in first person.
    - Headache: Person=1st
      - The entity is described in first person.
- There are some cases when DRUGS/SYMPTOMS/DISEASES are used as an indicator of other entity. In those cases the entity used for the reference should be annotated
  - Example: “The patient took ADHD prescription stimulants”
    - ADHD should be annotated as a SYMPTOM
    - “ADHD prescription stimulants” should not be annotated as there is no drug in the list that could be found by looking for that concept.
  - Example: “The patient received fatigue treatment”
    - “fatigue” should be annotated as a symptom.
    - “fatigue treatment” should not be annotated as there is no drug in the list that could be found by looking for that concept.

Attributes
- When an entity cannot be found in the list of concepts, “-1” will be used as the corresponding Entity Identifier.
  - All the annotations should have a value for the attribute Entity Identifier.
    - The -1 value can not be use for DRUGS (All annotated DRUGS have to be in Table A1).

Relations
- It is allowed to annotate relations between entities even if the related entities are not in the same sentence.
  - Example: “The patient took Adderall during the day. As a result the patient’s concentration improved”.
    - The entities to be annotated are Adderall (DRUG), and concentration (SYMPTOM). There will be a relation “outcome-positive” between these two entities even if each entity belong to a different sentence.

What _NOT_ to annotate?

Entities
- Entities should not both start and end with parenthesis.
  - In case this happens only the entity within the parenthesis will be annotated.
- DRUGS that are not listed in the Table A1 should not be annotated.
- In our annotations we don’t allow co-reference nor anaphoric references.
  - Example: “Geodon used to make me sleep...now with Adderall and Ritalin at night? Nope”
    - In that tweet “Nope” could be understood as “No sleep”, but we don’t annotate that concept because we don’t annotate anaphoric mentions.
  - Example: “Respondents used stimulants mostly for wakefulness and performance enhancement”
    - In this example “stimulants” is not listed among our drugs, so it should not be annotated
  - Example: “I took Geodon yesterday. It doesn’t work anymore”
    - In this sentence “It” could be understood as “Geodon”, but as we don’t allow
anaphora “It” will not be annotated.

- **EXCEPTION:** When an entity that has to be annotated contains an anaphoric mention to another entity to be annotated, the entity containing the anaphora should be annotated using that context information.
  - In the sentence "the patient experienced **Severe imbecility**, and that imbecility was intensified with the presence of […]" the second occurrence of "imbecility" refers to "Severe imbecility", and should be annotated as such (**Severe imbecility**, with ID=10040442).

**Attributes**

- If the DRUG is negated the relation will not be annotated.
  - Example: “I did not take prozac and now I don’t have a headache”
    - The relation between “prozac” and “headache” should NOT to be annotated.
  - If it is just the SYMPTOM/DISEASE what is negated we annotate the relation.
    - Example: “I took prozac and now I don’t have a headache”
      - The relation between “prozac” and “headache” has to be annotated.

- The attributes of the entities should not be included in the annotation span unless required by the tokenisation, or in case the entity is a concept per se.
  - Example: “nondiabetics” (annotate the entire word)
  - Example: “no pain” (annotate only “pain”)
  - Example: “probable chronic fatigue syndrome” (only annotate “chronic fatigue syndrome”).
  - Example: “**Severe dengue**” (annotate the 2 words as “severe dengue” is a concept recognized by MEDDRA)

- Determiners and quantifiers are never included in concept annotation unless that represents a different concept.
  - Example: “I took prozac and adderall and now I’m very tired”, the DISEASE is “tired”, not “very tired”.
    - In this case “very” will be encoded using the attribute “Severity”, setting it to “severe”.
  - Example: “The patient has **Severe imbecility**”
    - In this case “Imbecility” is a concept (ID=10021409), but “Severe imbecility” is a concept too (ID=10040442), so we would annotate “**Severe imbecility**”
      - In this case too “Severity” attribute will be “severe”.
## Appendix

| Drug Name | Brand name(s) |
|-----------|---------------|
| Lisinopril | Zestril, Zestoretic, Prinzeide, Prinivil, Tensopril |
| Prednisone | |
| Montelukast | Singulair, Pluralair, Montecarlolo-10, Montecarloflo, Lovetas |
| Triamcinolone acetonide | Kenalog, Volon A |
| Topiramate | Topamax |
| Dextroamphetamine sulphate | Adderall |
| Cortisone | Cortisone |
| Venlafaxine | Effexor, Trevilor |
| Buprenorphine | Suboxone, Cizdol, Subutex, Zubsolv, Bunavail, Temgesic, Buprenex, Norspan, Butrans |
| Sertraline | Zoloft, Lustral |
| Dextroamphetamine sulphate | Adderall |
| Methylphenidate hydrochloride | Ritalin, Concerta, Methylin, Medikinet, Equasym, Daytrana, Phenida, Attenta, Hynidate, Focalin |
| Modafinil | Modafinil, Alertec, Modavigil, Provigil |
| Citalopram | Citalopram, clexa, cipramil |
| Paroxetine | Paroxetine, paxil |
| Fluoxetine | Fluoxetine, prozac |
| Fluvoxamine maleate | Faverin, Fevarin, Floxyfrol, Luvox |
| Carbamazepine | Tegretol |
| Olanzapine | Zyprexa, Zypadhera, Lanzek |
| Trazodone | Depyrel, Desyrel, Mesyrel, Molipaxin, Oleptro, Trazodil, Trazorel, Trialodine, Trittico |
| Ziprasidone | Geodon, Zeldox, Zipwell |
| Ciprofloxacin | Ciprofloxacin |
| Levofloxacin | Levaquin, Tavanic |
| Moxifloxacin hydrochloride | Avelox, Avalox, Avelon, Vigamox, Moxeza |
| Quetiapine | Seroquel |
| Bevacizumab | Avastin |
| Melphalan | Alkeran, Sarcolysin |
| Rupatadine | Rupafin, Alergoliber, Rinialer, Pafinur, Rupax, Ralif |
| Tamoxifen | Nolvadex, Istubal, Valodex, Genox |
| Docetaxel | Taxotere |
| Seroquel | Quetiapine |
| Lamotrigine | Lamictal |
| Duloxetine | Cymbalta |
| Lisdexamfetamine | Vyvanse, Venvanse, Elvanse, Tyvense |

Table A1. Drug names and brand names of the targeted DRUGS.