InContext Annotation Protocol

## Installation of Hypothes.is

1. **Install** the[hypothes.is](http://hypothes.is) tool in your browser as an extension:<https://hypothes.is>
2. **Create** anaccount and login. <https://hypothes.is/signup>
3. **Join** the*dailymed* groupusing this link<https://hypothes.is/groups/pGv4X7iV/dailymed>
4. **View** the list of annotations here <https://hypothes.is/groups/pGv4X7iV/dailymed> or here <https://hypothes.is/stream?q=group:pGv4X7iV>

## InContext annotation protocol

1. **Go to** the[DailyMed](https://dailymed.nlm.nih.gov/dailymed/) product labels page using this link:<https://dailymed.nlm.nih.gov/dailymed/>
   1. Ensure that the Hypothes.is extension is active by hovering over the extension (small speech bubble-shaped box) at the right edge of browser (it must not be grayed out and must say that Hypothes.is is active when it is hovered over by the mouse pointer. If not, click it to make it active).
   2. Ensure that you are within the *dailymed* group. This will ensure that your annotations will appear within the group (and visible to other group members) and not elsewhere. To do this, click the Hypothes.is left arrow on the right of the browser window to open the Hypothes.is panel. At the top left of the panel, click the dropdown box and select “dailymed”.
2. **Annotate**! Select a drug from the list in the following sheets (preferably select one that has not been annotated yet): Cardiovascular drugs list: <https://docs.google.com/spreadsheets/d/14_mBEkNdoN0YAB44M8MgIbJKYFuJGlxdUXovItRq4qk/edit#gid=1688495677>, Antineoplastic drugs list: <https://docs.google.com/spreadsheets/d/14_mBEkNdoN0YAB44M8MgIbJKYFuJGlxdUXovItRq4qk/edit#gid=1576627653>.
   1. Depending on your choice of annotating a new drug or re-annotating an existing one, you should consider the following information:
      1. You can view the list of the annotated drugs by clicking on the group name in the Hypothes.is panel and selecting the View group activity and invite others section.
      2. If you are choosing to re-annotate an annotated drug, please select the reply icon in the bottom right corner of the desired annotation block in the Hypothes.is panel. Otherwise, yours will be the first annotation.
      3. When completing an annotation, please add your name next to the drug name in the above spreadsheets to enable tracking of progress for the annotated drugs.
      4. If re-annotating a drug, add your name in a new column next to the primary annotator’s name.
   2. Search for your selected drug in Step 6 on DailyMed by typing its name in the search box on the following page: <https://dailymed.nlm.nih.gov/dailymed/>
   3. Choose the first entry in the results list by clicking on it
   4. **Annotating the drug label:** we will guide you through the annotation process using CLOZAPINE as an example.
      1. Select the drug name title text (in this case CLOZAPINE) at the top of the DailyMed webpage for the selected SPL in Step 6c. You can do this by clicking and dragging over the entire title text. A drop down menu will appear providing two options: Annotate or Highlight. Click Annotate.
      2. A box window should appear on the right of the browser window with several options. At the top you will see the currently selected text that you want to annotate. Make sure the entire drug name has been selected so that you will see the exact drug name in this box.
      3. We will now annotate the drug name using its Drugbank ID. Go to <http://www.drugbank.ca/>. Search for the name of the drug in the main search textbox. In the result page you will see the Drugbank ID for the drug (in this case for CLOZAPINE it is DB00363).
      4. Now go back to the DailyMed webpage with the Hypothes.is window open and within the thin box (named “Add Tags”) enter the following tags:
         1. A tag called: “Label”
         2. A tag with the Drugbank ID of the drug obtained in Step 6d(iii) (in this case it will be DB00363).
   5. **Annotating the indications:**
      1. On the same DailyMed SPL webpage for the drug (e.g. CLOZAPINE), click on the “+” in front of the INDICATIONS and USAGE section. Select all the text under this section and copy it.
      2. Click on this link<https://bioportal.bioontology.org/annotator> and paste all the text inside the large textbox at the top of the page.
      3. In the “Select ontologies” textbox, select the Human Disease Ontology (DOID) and check the box: Match Longest Only. Click on the Get Annotations button.
      4. A table will appear at the bottom of the same page, with several fields. For each unique indication / disease term in the “Matched Class” column:
         1. Click the indication link
         2. A new page will appear with a table of information about the specific indication within the context of an ontology. Collect the following terms from the table on the right hand side of the page:
            1. DOID terms (starts with “DOID\_”)
            2. UMLS terms (starts with “UMLS\_CUI”)
         3. For example if we select the indication [schizophrenia](https://bioportal.bioontology.org/ontologies/DOID?p=classes&conceptid=http%253A%252F%252Fpurl.obolibrary.org%252Fobo%252FDOID_5419) in this case, we collect [DOID\_5419](https://hypothes.is/stream?q=tag:DOID_5419), [UMLS\_CUI:C0029838](https://hypothes.is/stream?q=tag:UMLS_CUI%253AC0029838) and [UMLS\_CUI:C0220702](https://hypothes.is/stream?q=tag:UMLS_CUI%253AC0220702). (in the case where there are multiple UMLS concepts, we collect all of them)
      5. For each unique disease mention found in Step 6e(iv):
         1. Go back to the DailyMed SPL webpage and highlight the condition that you want to annotate in the SPL text under “Indications & Usage” (it will most likely be the same term that you found under the “Matched Class” column in the NCBO annotator or a synonym of the term). In the case of CLOZAPINE, we have schizophrenia as an example. Make sure you select the entire word in the text. Two options will appear: Annotate or Highlight. Click on Annotate.
         2. Now the Hypothes.is window should open on the right (similar to what we saw in Step 6d(i)). Now inside the thin box (named “Add Tags”) enter the following tags:
            1. DOID tag : for each DOID term found for this highlighted condition, in Step 6e(iv), add a tag called “**DOID\_term**” to the Hypothes.is window on the SPL page, where “term” is the number identifier of the condition (do not leave any spaces). In our example, there is just one DOID term “DOID\_5419”. In some cases, you may not find the DOID term associated with an indication. In these cases, try to ensure that you at least find a UMLS term if possible (or see Step 6e(vii-viii)).
            2. The UMLS tags: for each UMLS term found for this highlighted condtion, in Step 6e(iv), add a tag called “**UMLS\_CUI:term**” to the Hypothes.is window on the SPL page, where “term” is the number identifier of the condition (do not leave any spaces). In our example, we have two terms: [UMLS\_CUI:C0029838](https://hypothes.is/stream?q=tag:UMLS_CUI%253AC0029838) and [UMLS\_CUI:C0220702](https://hypothes.is/stream?q=tag:UMLS_CUI%253AC0220702).
            3. Tag indication or contraindication: **This part is critical**:

If by reading the surrounding text of the disease mention in the SPL, it appears that the drug treats this condition: Enter a tag called indication

If there is evidence in the text that suggests that the drug should not be used for that condition: Enter a tag called contraindication.

* + - * 1. Tag disease modifying (DM) or symptomatic (SYM):

If the text states that the drug directly treats the primary condition tagged in Step 6e(v)1., enter a tag called DM.

If the drug treats some condition arising out of the primary condition (such as a symptom), enter a tag called SYM. E.g. If CLOZAPINE treats schizophrenia which is the primary indication under consideration, enter DM. If CLOZAPINE treats hypertension which arises out of schizophrenia and the indication under consideration is schizophrenia, enter SYM.

* + - * 1. Tag confirmed or rejected:

If it is clear from the text that the drug treats the condition under consideration, enter a tag called confirmed.

If it is clear from the text that the drug has no association with the condition, or does not treat it (sometimes the condition may appear in the text under Indications and Usage but it is irrelevant to the drug use case), enter a tag called rejected

* + 1. Now go back to Step 6e. and replace Step 6e(iii) with this one: keep the “Select ontologies” box blank. In the Select “UMLS Semantic Types” box,select “Disease or Syndrome (TO47)” and keep the “Match Longest Only” checkbox clicked. RepeatSteps 6e(iv-v) for all unique disease mentions again.This step is necessaryto recover any additional indications which may have been missed by restricting ourselves to the Human Disease Ontology earlier.
    2. If you are unable to find UMLS terms for a particular disease mention up to this point, go to this link<https://uts.nlm.nih.gov/metathesaurus.html> and use the UMLS term browser to look up the indication. (You will need to sign up for an account to access this application). Once signed up and signed in, go to the link above. In the “search” tab of the browser, make sure the “Term” radiobutton is selected. Type in the text name of the disease mention and click “Go”. A list of UMLS CUIs will appear below the input box together with the textual descriptions of these terms. Choose the UMLS CUI which has the **highest** **match** withthe input term, in terms of **specificity**. E.g. if the disease mention in an SPL is “Incipient Schizophrenia” then we would choose UMLS\_CUI:C0021151 over UMLS\_CUI:C0036341
    3. If at this point, there are still no appropriate DOID or UMLS terms for the disease mention under consideration, add a tag called “missing”. This will be investigated later.
  1. **Annotating the medical context information:** this includes items such as co-therapies (medical procedures/therapy that does not involve administration of specific drugs), co-prescribed medications (medication advocated to be used alongside the primary drug in this SPL), co-morbidities (conditions mentioned in the SPL that often occur together in patients with the primary condition treated by the drug), genetic (patients with specific genetic mutation for which the drug is indicated), and temporal conditions of taking the drug (e.g. information in the SPL which explains when the drug should, or should not, be taken). This latter type can refer to a certain time period, for example: “2 hours after a meal”, a specific life phase “not during pregnancy”, or an age range: “only in patients between the ages of 2-4 yrs old”.
     1. Co-therapies: highlight the name of the therapy in the SPL text, Click Annotate. Add a tag called “role:co-therapies”, a tag called “UMLS\_CUI:term” where “term” is the identifier of the co-therapy that is prescribed in combination with the drug for this indication, according to information in the SPL text.
     2. Co-prescribed medications: highlight a medication in the SPL text, Click Annotate. Add a tag called “role:co-prescribed medications”, a tag with the Drugbank ID of the medication e.g. DB01073, and a tag called “UMLS\_CUI:term” where “term” is the identifier of the co-prescribed medication in combination with the drug for this indication, according to information in the SPL text.
     3. Co-morbidities: highlight a disease mention in the SPL that clearly represents an indication for the drug. Click Annotate. Add a tag called “role:co-morbidities”. Add another tag called “UMLS\_CUI:term” where “term” is the identifier of the condition in the text that represents a co-morbidity of the primary disease mention in the SPL text.
     4. Genetic: highlight a genetic mention in the SPL. Click Annotate. Add a tag called “role:genetic”. Add another tag called “UMLS\_CUI:term” where “term” is the identifier of the mention in the text that represents a genetic factor important in the indication of the disease in the SPL text.
     5. Temporal information: highlight the name of the indication or medication. Add a tag called: “role:temporal aspects”. Add another tag capturing the temporal information about the usage of the drug (as specified in the SPL text) e.g. “2 hours before sleeping” , “age range: < 70 yrs”, “disallowed:pregnancy” etc.