

I am working on defining a model for how to fully represent clinical indications, including qualifiers about the specific type of disease and how it is approved to be used. This will be used for structuring and generating drug indications for FDA and EMA approved and orphan drugs and adding them to Wikidata, and could also be used in the context of the Translator.

SNOMED CT and ICD-11 both have well-defined models for defining clinical findings (encompassing diseases, symptoms, phenotypes), but don't (as far as I can tell) model an *indication*, more specifically than specifying a therapeutic role (e.g. propranolol -> non-selective beta-blocking agent)

I've outlined a rough draft of a model below. It incorporates a subset of the properties used to represent clinical findings in SNOMED CT and ICD-11, in addition to several more I've added.

To get an idea of what "fully represent a clinical indication" means, here are some examples in which a single "treats" property is not sufficient to capture all of the knowledge in the statement:

- First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions
- Suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older
- For adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein.

Data Sources

- FDA approved indications
 - Data source: OpenFDA <https://open.fda.gov/>
 - Data comes from drug labels. Example: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0002ad27-779d-42ab-83b5-bc65453412a1>
- FDA Orphans indications
 - <http://www.accessdata.fda.gov/scripts/opdlisting/opa/listResult.cfm>
- EMA Approved
 - Only lists "therapeutic area", which doesn't usually contains the detailed information as I'm describing here
 - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124
- EMA Orphan
 - <http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>
- MEDI--an Ensemble MEDication Indication Resource

- <https://medschool.vanderbilt.edu/cpm/center-precision-medicine-blog/med-ense-mble-medication-indication-resource>

Attributes used to define Clinical Finding concepts in SNOMED CT

http://doc.ihtsdo.org/download/doc_EditorialGuide_Current-en-GB_INT_20150131.pdf (Page 79-81)

- **Finding site:** the body site affected by a condition
- **Associated morphology:** morphologic changes seen at the tissue or cellular level that are characteristic features of a disease (metastatic, enlarged...)
- **Associated with:** clinically relevant association between concepts without either asserting or excluding a causal or sequential relationship between the two. Values: Clinical Finding, Procedure, Event, Organism, Substance, Physical object, Physical Force, Pharmaceutical / biologic product
 - **Causative agent:** identifies the direct causative agent of a disease
 - **Due to:** used to relate a | Clinical finding | directly to its cause
 - **After:** used to model concepts in which a clinical finding occurs after another clinical finding or procedure
- **Severity:** mild, moderate, stage 3
- **Clinical course:** course and onset of a disease (Sudden onset, Chronic, Acute, etc.)
- **Episodicity:** represent episodes of care provided by a physician or other care provider (e.g. first episode)
- **Occurrence:** specific period of life during which a condition first presents. (e.g. Childhood)
- **Finding method:** specifies the means by which a clinical finding was determined.
- **Finding informer:** person or other entity from which the clinical finding information was obtained

Parameters for the Content Model in ICD-11

- http://www.who.int/classifications/icd/revision/Content_Model_Reference_Guide.January_2011.pdf
- <https://wiki.nci.nih.gov/download/attachments/25136344/BMIR-2010-1405.pdf>
- ICD-11 Content Model in UML: <http://icd11model.github.io/>
- **Body System/Structure Description** - anatomy and physiology
- **Temporal Properties** - acute, chronic or other
- **Severity of Subtypes Properties** - mild, moderate, severe, or other scales
- **Manifestation Properties** - Manifestation of a dysfunction either identifiable by the affected person or the health worker
- **Causal Properties** - etiology: infectious, external cause, etc.
 - Agents, Mechanisms, Risk Factors, Genomic
- **Functioning Properties** - impact on daily life: activities and participation
- **Specific Condition Properties** - relates to pregnancy etc.

- **Treatment Properties** - specific treatment considerations: e.g. resistance
- **Diagnostic Criteria** - logical rules to identify a particular disease

Greg's Version for Defining Drug Indications

The following properties should be used to define the disease itself and not used as qualifiers on the indication

- located in
 - equivalent to: Finding site (snomed), Body System/Structure (ICD-11)
 - E.g.: lung adenoma = adenoma *and located in some* lung
- Temporality/Has clinical course
 - Equivalent to: Clinical course (snomed), Temporal (ICD-11)
 - Allowed values: http://purl.obolibrary.org/obo/HP_0000004
 - E.g. childhood onset, acute, chronic, progressive
 - "**childhood onset** epileptic encephalopathy" DOID_0060475
- Severity
 - Equivalent to: Severity (snomed), Severity of Subtypes (ICD-11)
 - E.g. mild, moderate, severe
 - "**severe** pre-eclampsia" DOID_13129
- Treatment consideration
 - Equivalent to: ??? (snomed), Treatment Properties (ICD-11)
 - e.g. **Insulin-resistant** diabetes, "**multidrug-resistant** tuberculosis" DOID_401, "**malignant** pleural mesothelioma" DOID_7474

The following properties should be used to to qualify a drug indication

- Caused by / due to / associated with
 - equivalent to: associated with (snomed), Causal (ICD-11)
 - Allowed values: Substances, organisms, objects, events, Pharmaceutical / biologic product, Predisposing or causing genes, risk factors, inheritance
 - E.g.
 - "Treatment of chronic iron overload **due to blood transfusions**" (event/procedure)
 - "chronic pulmonary infections **due to Pseudomonas aeruginosa**" (organism)
 - "treatment of patients with unresectable or metastatic melanoma **with BRAF V600E mutation**" (genetic factor)
- Occurrence / specific condition
 - Equivalent to: Occurrence (snomed), Specific Condition?? (ICD11)
 - Allowed values: period of life, gender, other specific phenotypes
 - E.g. during pregnancy, male, female, child
 - "Indicated in **adult males** with deficient spermatogenesis due to hypogonadotropic hypogonadism"

metastatic non-small cell lung cancer (term doesn't exist, subclass of "non-small cell lung carcinoma")

- Use / As: first-line treatment
- Caused by: EGFR exon 19 deletion ([Q28381469](#)) (civic ID [133](#))

Suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 6 years and older

Recurrent bronchopulmonary infections (HP_0006538) ??

- Use / As: Suppressive
- Caused by: Pseudomonas aeruginosa ([Q31856](#))
- Occurrence / specific condition: child (D002648, Q7569), Adolescent (D000293), adult (D000328, Q80994)

for the prevention and treatment of nausea, vomiting, or dizziness associated with motion sickness

Motion sickness (DOID_2951)

- Manifests as: [Nausea](#) (HP_0002018), [vomiting](#) (HP_0002013), [dizziness](#) (HP_0002321)
- Use / As: prevention, treatment

Properties describing clinical finding

Clinical Course -> Courses (288524001)

Grade -> Grades (258349007)

Occurrence -> Periods of life (282032007)

Episodicity -> Episodicities (288526004)

Associated With ->

Procedure (71388002)

Organism (410607006)

Substance (105590001)

Pharmaceutical / biologic product (373873005)

Disease

Used in combination with -> Pharmaceutical / biologic product (373873005)

Describing indication

Has Intent -> Intents (363675004)

Extra

IndicationText -> The relevant section, if there are multiple (free text)

Missing -> Free text