INTERNATIONAL RXNORM EXTENSION

to support the expansion of the OHDSI research network beyond the US

1. Background

The OHDSI research network started as a scientific collaboration out of Columbia University in New York, USA. However, international participant involvement would greatly benefit this network for a number of reasons. First, it is our belief that clinical research is a global, as the similarities between populations in different parts of the world may outweigh the differences. Second, the solution of many clinical research problems requires well-validated samples in order to develop standards that effects might be weak, biased or happen in the shadow of a strong background. Therefore, a network that spans different cultural and healthcare systems allows avoiding biases and understanding the effects introduced by those healthcare systems and distinguishing them from the biological effects on the outcomes of treatment or care.

Such an expansion to international participants creates the need to get the data into the OHDSI Common Data Model. Part of it is the ability to define the semantic content of the data through the ONCOP Standardized Vocabulary, which is commonly known as “Mapping.” This mapping consists of:

1. Mapping of Coding Schemes: a set of Standard Concepts, or

2. Creating new Standard Concepts and incorporating them into the existing hierarchy.

The amount and nature of the effort required for such an effort is very different between the different Domains. Conditions are usually “International,” as people generally have the same diseases, and there is an international motive to define them ICDs and their modifications (ICD-10 for the USA and ICD-10 for the UK) and SNOMED CT. However, much effort has been done to capture concepts describing the exposure of patients to drug products available on local markets, the knowledge of the content of these products, and their categorization in classification systems. These local markets are governed by the authorities of the countries (even though there is some harmonization efforts going on), and as a result there are common products at one side of the world, but drugs do exist on a local market or a single market.

2. Solution: Make RxNorm for the World

We created a system that can add any international systematic drug terminology to the existing RxNorm implementation in the Standardized Vocabularies. Note that this implementation differs in its format from the original provided by the NLM, but having its concept or logical entity intact.

- Active Ingredients not approved for marketing in the US are added
- Dose Forms not used in the US are added, which is common
- Brand Names not used in the US are added
- Additional attributes are added that are necessary to project foreign drug markets:
  - Drug Class: Prescription drugs are mostly pre-packaged to standardized products, similar to the situation in the US.
  - Authentic Reference: the US.”
  - Bioavailability: in the US. Therefore, it is necessary to capture this attribute in the RxNorm Extension, as prescription orders generally don’t contain a variable of changing amount.
  - Expiry: the US.
  - Volume of package: in the US.

Supplier/film does not have a concept, even though the IND concept does; in international markets, this attribute is also essentially the same, except the specific values are unique.

- All relationships between Concepts, which cross between RxNorm and RxNorm extension depending on whether or not attributes exist in the other.

- Relationships to classification systems such as ICD.

Additionally, some new vocabulary “Pattern Extension” is created containing all the attributes as specified above. The RxNorm and the RxNorm extension vocabularies together form a comprehensive Drug Domain able to list the drug market of any country and therefore the patient data containing the drug exposure in this market.

3. RxNorm Extension development and building

3.1 First, we consider any drug concept as a set of Attributes, for example:

- **Identification** (active ingredient, brand name, strength).
- **Dose Form**.
- **Brand Name**.
- **Active**.

3.2 Mapping attributes to corresponding ones in RxNorm. For more than one may correspond, use precedence which represents the degree of similarity to RxNorm.

3.3 Match: Compare drug concepts in existing vocabularies (RxNorm and RxNorm extensions) by matching attributes

- Ingredients by precedence

- Dose Form by precedence (on a current example: "Solution/Injection" to "Dose Form" for given process/combination)

- Brand Name by precedence

3.4 Build: for all non-matching concepts to create Hierarchy Extension

4. Hierarchy and Structure

5. Results

Current RxNorm Extension Source Vocabularies Summary

The RxNorm Extension already contains drug names from drug markets of: Canada (DRG), US (EMMES), France (BOPM), Germany (AMTS) and Australia (AMTS). Drug markets will be covered in the nearest future: Belgium (BOM), Japan (JDRG).

 RxNorm Extension extends at different degree into the four attributes:

- Ingredients: There are 15,000 new ingredients, but most of them are herbal medicines or homeopathic preparations, in rare cases, new FDA-approved compounds are added, such as Aromatase Inhibitor, Cefotaxime, Bicenten, etc.

- Suppliers: Most of the Suppliers are country-specific, with large multinationals pharmaceuticals comprising a small portion only. Also, those international companies have marketing agreements with local companies allowing them to sell drugs under the same brand name. For example, Brande initially developed by Lippert and then distributed in other markets by variety of other pharmaceutical companies, such as Pfizer, BMS, Novo, Merck, AbbVie, Merck, etc.

- Dose Form: Dose Form covers most of the conventional Dose Forms, except some special cases such as oral liquid or injectable doses, or those that are usually categorized as devices, such as intravenous drug delivery systems.

- Brand Name: Most of the 44 thousand new Brand Names are country specific, with few reserved terms/numbers such as "Generic", "Omeprazole", "Domperidone", etc.

For example, to find all patients using products containing Atenolol, the hierarchy (ingredient, anesthetics) table can be used to traverse the RxNorm or RxNorm Extension drugs containing Atenolol (Fig. 4). If the original country-specific source codes are needed for quality checks, they can be found along the "Map to/Map from" relationships in the concept/relationship table. This approach performs at a much more efficient rate than the conventional keyword search for brand names or non-standardized ingredient names in the descriptors of the source code reference tables (Delekis L, Baus BRJ, Sosolilac M. Health Serv Outcomes Res Methods 2013 Mar;13(1):8-17).

6. Conclusion

- RxNorm Extension has 5 drug markets covered:
  - Canada, Germany, Canada, and Australia
  - Significant to drug distribution in the world that makes RxNorm Extension extremely needed for worldwide drug markets and corresponding patient data analysis.