Evaluation of RxNorm for Medication Clinical Decision Support

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Abstract

We evaluated the potential use of RxNorm to provide standardized representations of generic drug name and route of administration to facilitate management of drug lists for clinical decision support (CDS) rules. We found a clear representation of generic drug name but not route of administration. We identified several issues related to data quality, including erroneous or missing defined relationships, and the use of different concept hierarchies to represent the same drug. More importantly, we found extensive semantic precoordination of orthogonal concepts related to route and dose form, which would complicate the use of RxNorm for drug-based CDS. This study demonstrated that while RxNorm is a valuable resource for the standardization of medications used in clinical practice, additional work is required to enhance the terminology so that it can support expanded use cases, such as managing drug lists for CDS.

Introduction

Clinical decision support systems (CDSS) have emerged as an essential component of clinical information systems and electronic medical records (EMRs). Not only do CDSS serve a variety of functions to assist clinicians provide better care and prevent adverse events, but also they are required to meet regulatory requirements including the Meaningful Use measures of the American Recovery and Reinvestment Act (1). A number of health care organizations have described positive outcomes associated with deploying CDSSs and have leveraged their capabilities as a strategic tool for attaining institutional quality and safety improvement goals and objectives (2-4). Despite the growing advantages associated with CDSS, however, significant challenges impede its widespread adoption and the development of even more sophisticated computerized alerts and types of CDSSs (5). Sittig et al. identified ten grand challenges associated with CDSSs, which included improving the user interface to streamline clinical workflow and disseminating best practices for CDS design, development, and implementation (6). Fine-tuning CDS rules to deliver the most useful information at the appropriate time without causing alert fatigue remains a significant challenge, particularly when medications are involved (7).

One of the primary challenges related to the implementation of a robust, scalable CDSS for medications is the development of a comprehensive knowledge base that effectively accommodates maintenance and interoperability, supports rigorous data quality management principles, and enables the development of "free form" rules that are EMR-agnostic and accessible to ancillary medication management and supporting systems (8). In an effort to more effectively manage our medication-related CDS rules, including those related to pharmacogenomics, across the diverse systems within the Mayo Clinic enterprise we sought to adopt a standard, vendor-neutral drug terminology that would support interoperability and allow us to manage a single drug list for each CDS rule that is implemented. This manuscript describes our evaluation of RxNorm to better understand its capabilities and limitations in the context of a prototypic use case: the management of the drug list for an existing, active CDS rule.

Motivating Use Case: CDS Rule for Deep Vein Thrombosis (DVT) Prophylaxis

The following scenario illustrates a motivating use case for this study. To minimize the maintenance of drug-based CDS rules as formularies change, medications are referenced by generic drug name. To minimize alert fatigue and improve the specificity of the rules, the route of administration is used as an additional criterion for the rule trigger.

A CDS rule was developed to ensure that hospitalized inpatients receive deep vein thrombosis (DVT) prophylaxis. Providers receive a pop-up alert in the ordering system if no DVT prophylaxis was ordered.

The rule scans the active order list to determine if an order for heparin exists, using an RxNorm identifier (RxCUI) for heparin injectable solution. Testing reveals the rule is not identifying some orders for heparin subcutaneous injection. After detailed review of the data, it is determined that the RxCUI used for heparin injectable solution is not used for heparin in a prefilled syringe.

In this example, a logical assumption was made that all products that were injectable solutions for a given drug would have that corresponding defined relationship. In reality, drugs that were available in prefilled syringes were assigned a different relationship than those that were not in prefilled syringes. Regardless of the reason for this difference, this example emphasizes the necessity of knowing the intricacies and limitations of the data source, especially when used for clinical applications.

Background

RxNorm is a standard terminology developed by the National Library of Medicine (NLM) that provides normalized names for clinical drugs (9). It is intended to be used to facilitate the exchange of medication-related information among clinical systems and it is part of the federal Meaningful Use standard. RxTerms is a drug interface terminology that is derived from RxNorm, intended to facilitate medication order entry. It contains a pruned set of drugs from RxNorm that are anticipated to be most useful in a prescribing environment (10).

The Veterans Affairs National Drug File Reference Terminology (NDF-RT) is developed by the Department of Veterans Affairs (VA) Veterans Health Administration (11). The NDF-RT contains information about drug characteristics, including ingredient(s) and dose form. Concepts in the NDF-RT are organized into taxonomies, which represent generalization relationships between concepts hierarchically. As of June 2010, the NDF-RT has been integrated into RxNorm.

The RxNorm and NDF-RT terminologies have been used extensively for the normalization of drug data (12-15). Many of these efforts focused on developing methods for mapping terms from local drug coding systems to the reference terminologies and assessing the overall coverage of content. In contrast, in this study we evaluated the ability of RxNorm, with associated data from relationships to NDF-RT and RxTerms, to provide standardized representations of drug name and route of administration to facilitate management of drug lists for CDS rules.

Materials and Methods

Data Sources

The RxNorm full monthly release dated February 3, 2014 was downloaded from the NLM Unified Medical Language System (UMLS) web site (16). The RxTerms data files, version 201401, were also downloaded (17). The RxNorm and RxTerms data were loaded into a local MySQL database using a custom version of the loader scripts that were provided. The "rxnconso" and "rxnrel" tables were cloned and populated with subsets of the original data from the respective tables to facilitate complex queries that required multiple joins across these tables.

Terms from the NDF-RT "Dose Forms" (NUI N0000010010) hierarchy that had the NDFRT_KIND property of "DOSE_FORM_KIND" were downloaded via the NLM NDF-RT REST API using http://rxnav.nlm.nih.gov/REST/Ndfrt/allconcepts?kind=DOSE_FORM_KIND. The NDF-RT unique identifier (NUI) was extracted for each term. Since the term "Dose Forms" contains two child hierarchies, "Drug Delivery Device" (NUI N0000177905) and "Orderable Drug Form" (NUI N0000135762), the BioPortal web interface (18, 19) was used to browse the NDF-RT terminology and determine the branch to which each dose form term belonged. The concept terms, codes, and hierarchical branch name were loaded into a custom table in the local database.

Identification of Clinical Drugs and Related Attributes

To evaluate RxNorm for our motivating use case, we needed to identify the term types (TTY) that corresponded to generic drug name and route of administration. The RxNorm technical documentation was used to determine which entities and relationships were most pertinent to this study (20, 21). We chose the Semantic Clinical Drug (SCD) to represent orderable drugs using generic drug name(s). The SCD also contains strength and dose form. The local RxNorm database was queried for all SCDs (TTY = "SCD") that did not have a "suppress" attribute of "O", "Y", or "E". This list of drugs was used as the starting point for evaluation.

By browsing the RxNorm data using the RxNav user interface (22), several attributes were found to contain information related to route of administration: "Dose Form" and "Dose Form Group" from RxNorm; "rxn_dose_form", "new_dose_form", and "route" from RxTerms; and "Dose Form" from NDF-RT (**Figure 1**). The NLM was contacted to clarify the relationship between these attributes. RxNorm Dose Form was originally based on HL7 vocabulary group dose forms. RxNorm Dose Form was equivalent to RxTerms rxn_dose_form, which was used to derive RxTerms route and new_dose_form. RxTerms route was used as the basis for RxNorm Dose Form Group. NDF-RT Dose Form was "initialized from RxNorm" but equivalency was not determined. Based on this

information, the attributes RxTerms rxn_dose_form and RxNorm Dose Form Group were omitted from the analysis but the other attributes were retained and used for comparison.

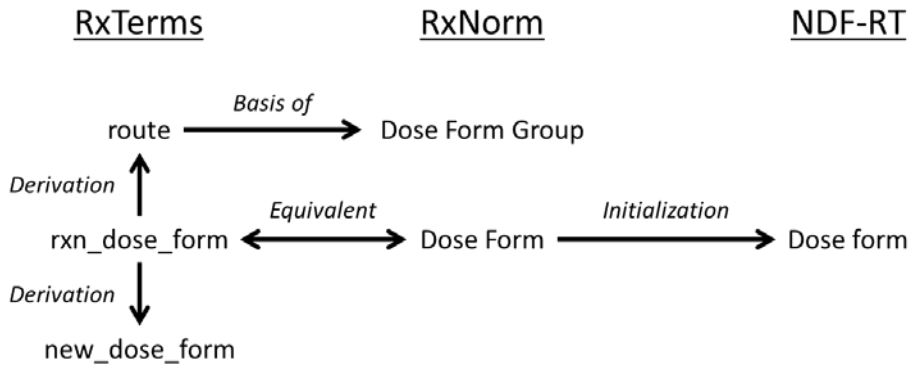

Figure 1: Attributes containing route of administration. The figure shows the attributes from each of the three data sources that were found to contain information related to route of administration, as well as the relationship between those terms.

Extraction and Evaluation of Defined Relationships

Instances of RxNorm Dose Form (TTY = "DF", source abbreviation (SAB) = "RXNORM") were obtained for each SCD using the RxCUI of the SCD and the relationship (RELA) "has_dose_form" (**Figure 2**). Terms for RxTerms route and new_dose_form were extracted directly from the RxTerms data using the RxCUI of the SCD. Terms for NDF-RT Dose Form (TTY = "PT", SAB = "NDFRT") were obtained for each SCD using the RxCUI of the SCD and the relationship (RELA) "dose_form_of". The resulting data set from each source was checked for missing or multiple terms for each SCD. All related terms were stored in new tables in the database to simplify subsequent analysis and exported to a spreadsheet for manual review of inter-source semantic consistency.

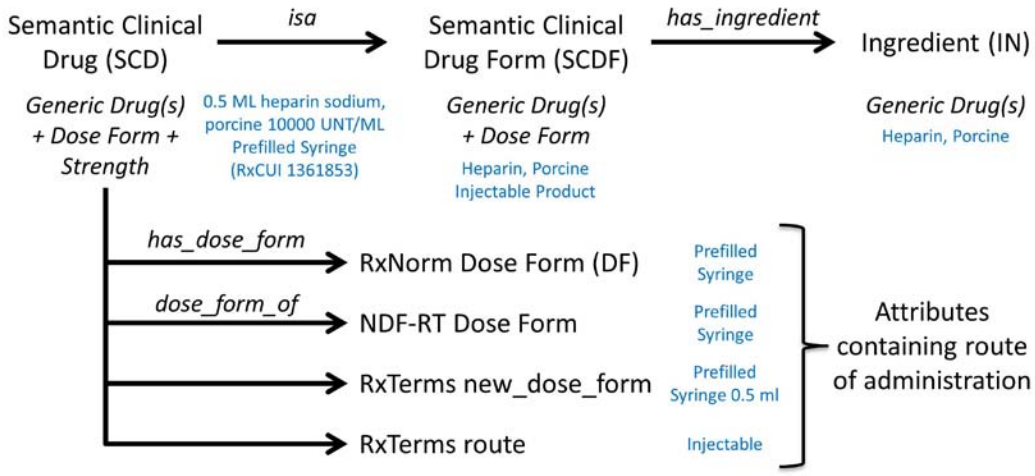

Figure 2: Drug entities, attributes, and relationships. The figure shows the entities, attributes, and relationships that are relevant to this study. Terms corresponding to the heparin use case are shown in blue text, as examples.

The Semantic Clinical Drug Form (SCDF) was used to compare dose forms for a given set of ingredients. The SCDFs (TTY = "SCDF"; "suppress" attribute not "O", "Y", or "E") associated to each SCD were obtained using the RxCUI of the SCD and the relationship (RELA) "isa". Ingredients (TTY = "IN", SAB = "RXNORM") for each

SCDF were obtained using the relationship (RELA) "has_ingredient". An ordered, concatenated form of ingredients was created for each SCD. Similarly, an ordered, concatenated list of dose forms was generated for each concatenated ingredient.

Results

Identification of Clinical Drugs and Related Attributes

The SCD contains generic drug name(s), strength, and dose form, and as such it serves as a convenient entity in RxNorm to which orderable drugs can be mapped. We found 20,268 SCDs in RxNorm, which were used as the starting point for the subsequent evaluation.

The authoring and maintenance of drug lists for CDS rules is most efficiently performed using the ingredient generic name and route of administration; therefore, it was necessary to obtain these attributes for each SCD. Generic ingredients were clearly represented within the RxNorm data model (TTY = "IN") but information about the route of administration was found in several entities (**Figure 1**). Two of these were eliminated from further consideration. Specifically, RxTerms rxn_dose_form was found to be redundant with RxNorm Dose Form, and was excluded from further analysis. Similarly, RxNorm Dose Form Group was defined as "a term type that serves as a grouping of dose forms (TTY=DF) related by route of administration (i.e., Topical) or dose form (i.e., Pill)" (23) and was also excluded since it was a less primitive concept than its source concepts, which were already included in the analysis.

Extraction and Evaluation of Defined Relationships

The RxNorm Dose Form was identified for each SCD in the data set. A total of 20,268 Dose Form terms were found, one for each SCD. No SCD had more than one RxNorm Dose Form and no SCDs were missing a related Dose Form. There were 104 different terms represented; the most frequently used terms are shown in **Table 1**.

RxCUI	Dose Form	Frequency
317541	Oral Tablet	4223 (20.8%)
316949	Injectable Solution	4215 (20.8%)
316965	Oral Capsule	1950 (9.6%)
316968	Oral Solution	1439 (7.1%)
316945	Extended Release Tablet	723 (3.6%)
721656	Prefilled Syringe	594 (2.9%)
316982	Topical Cream	589 (2.9%)
316969	Oral Suspension	512 (2.5%)
316986	Topical Solution	505 (2.5%)

Table 1: RxNorm and NDF-RT Dose Form. The most frequently used terms are listed for RxNorm and NDF-RT Dose Form.

The terms for RxTerms route and new_dose_form were extracted for each SCD. Only 15,077 SCDs had related terms from RxTerms (exactly one route and new_dose_form each); 5191 SCDs (25.6% of the SCDs in the data set) were missing corresponding terms from RxTerms. The most frequently used terms for route and new_dose_form are shown in **Table 2**; a total of 39 and 170 distinct terms were found, respectively.

route	Frequency
Oral Pill	6167 (40.9%)
Injectable	3754 (24.9%)
Topical	1584 (10.5%)
Oral Liquid	1510 (10.0%)
Chewable	305 (2.0%)

new_dose_form	Frequency
Sol	4820 (32.0%)
Tab	3954 (26.2%)
Cap	1667 (11.1%)
Susp	564 (3.7%)
Cream	396 (2.6%)

Table 2: Terms from RxTerms. The most frequently used terms are listed for RxTerms route and new_dose_form.

NDF-RT Dose Form terms were extracted for each SCD. Although we expected at most 20,268 results, 20,417 related terms were found. Further investigation revealed that 55 SCDs were related to two NDF-RT Dose Form terms and 47 SCDs were related to three terms. The 251 terms related to these 102 SCDs were instances of only 7 different terms that represented three distinct concepts: mouthwash, toothpaste, and topical cake (**Table 3**). Specifically, 47 SCDs were related to the NDF-RT orderable drug form "mouthwash", but they were also related to similar terms from two other NDF-RT hierarchies (pharmaceutical preparations and chemical ingredients). Similarly, 54 SCDs were related to the orderable drug form "toothpaste" as well as the chemical ingredient "toothpastes". A single SCD contained relationships to two terms from the orderable drug from hierarchy: the concept "cake" and its child concept "topical cake".

NUI	Concept	Location in NDF-RT Hierarchy
N0000029230	MOUTHWASHES	Pharmaceutical Preparations => Drug Products by VA Class => Dental and Oral Agents, Topical
N0000135733	Mouthwash	Orderable Drug Form => Liquid => Solution => Oral Solution
N0000011404	Mouthwashes	Chemical Ingredients => Biomedical and Dental Materials
N0000135791	Toothpaste	Orderable Drug Form => Solid => Paste
N0000171562	Toothpastes	Chemical Ingredients => Biomedical and Dental Materials => Dentifrices
N0000135686	Cake	Orderable Drug Form => Solid
N0000184140	Topical Cake	Orderable Drug Form => Solid => Cake

Table 3: Terms for NDF-RT Dose Form. The table lists groups of terms for NDF-RT Dose Form that were related to a single SCD.

All SCDs were related to a single term for Dose Form that was in the orderable drug form hierarchy, except for one SCD that contained relationships to both "cake" and "topical cake". When the extraneous terms from the pharmaceutical preparations and chemical ingredients hierarchies, and the parent concept "cake", were excluded from the query 20,268 results were obtained. Each SCD was found to contain exactly one term for NDF-RT Dose Form. There were 104 different terms represented; the terms and their frequencies were identical to those for RxNorm Dose Form (**Table 1**).

Since each SCD was related to at most one term of each type (RxNorm Dose Form, RxTerms route and new_dose_form, NDF-RT Dose Form), the results of the individual searches were merged into a single table that was indexed by SCD. The semantic consistency of the terms from each data source was reviewed by examining all 296 unique combinations of terms. Only 88 combinations were found to be consistent, which was defined to allow for some semantic precoordination of concepts. In 125 cases the terms from RxTerms were narrower than those from RxNorm and NDF-RT due to the explicit inclusion of route, count, and/or quantity information (**Table 4**). The remaining 83 combinations, corresponding to 5191 SCDs, were missing terms from RxTerms. In all cases, the terms for RxNorm Dose Form and NDF-RT Dose Form were identical.

RxNorm Dose Form	NDF-RT Dose Form	RxTerms route	RxTerms new_dose_form
Dry Powder Inhaler	Dry Powder Inhaler	Inhalant	DPI 60 puff
Extended Release Capsule	Extended Release Capsule	Oral Pill	24 HR XR Cap
Augmented Topical Lotion	Augmented Topical Lotion		
Augmented Topical Lotion	Augmented Topical Lotion	Topical	Lotion (Augmented)
Buccal Tablet	Buccal Tablet		
Buccal Tablet	Buccal Tablet	Buccal	Tab
Medicated Shampoo	Medicated Shampoo		
Medicated Shampoo	Medicated Shampoo	Shampoo	Medicated Shampoo

Table 4: Examples of semantic consistency among terms. The first two rows illustrate the inclusion of qualifiers (e.g., "60 puff", "24 HR") in the terms from RxTerms that are not present in those from RxNorm or NDF-RT. The remaining rows show pairs of term combinations that contain identical values for RxNorm and NDF-RT but differ overall because one of the entries is missing terms from RxTerms.

Of the 83 combinations that lacked terms from RxTerms, 76 were found to have an equivalent entry based on RxNorm and NDF-RT values that also contained terms from RxTerms (**Table 4**). These 76 instances corresponded to 5065 SCDs, which accounted for 97.6% of SCDs that were missing terms from RxTerms and 25.0% of all SCDs in this data set. For the remaining 7 combinations, which corresponded to 126 SCDs, a corresponding entry either was not found or could not be assigned due to ambiguity as a result of the semantic precoordination of route, count, or quantity (**Table 5**).

# SCDs	RxNorm Dose Form	NDF-RT Dose Form	RxTerms route	RxTerms new_dose_form
1	Crystals	Crystals		
2	Metered Dose Inhaler	Metered Dose Inhaler		
1	Ophthalmic Cream	Ophthalmic Cream		
1	Otic Ointment	Otic Ointment		
13	Prefilled Applicator	Prefilled Applicator		
107	Prefilled Syringe	Prefilled Syringe		
1	Rectal Solution	Rectal Solution		

Table 5: Missing terms from RxTerms. Term combinations that were missing terms from RxTerms. These combinations did not have an unambiguous corresponding entry that could be used to obtain these terms.

To evaluate the consistency of related terms at the drug level, generic ingredients (IN) were obtained for each SCD. Since there was no direct relationship between SCD and IN, the SCDF was used as an intermediate step. The SCDF, which contain generic drug name(s) and dose form but not strength (**Figure 2**), was obtained for each SCD. Each SCD had exactly one SCDF; 8717 distinct SCDFs were retrieved. The majority of SCDFs (4763, 54.6%) were utilized by a single SCD, which indicated that only one strength was available for the drug in the specified dose form (**Figure 3**). Another 1705 (19.6%) SCDFs were used by two SCDs.

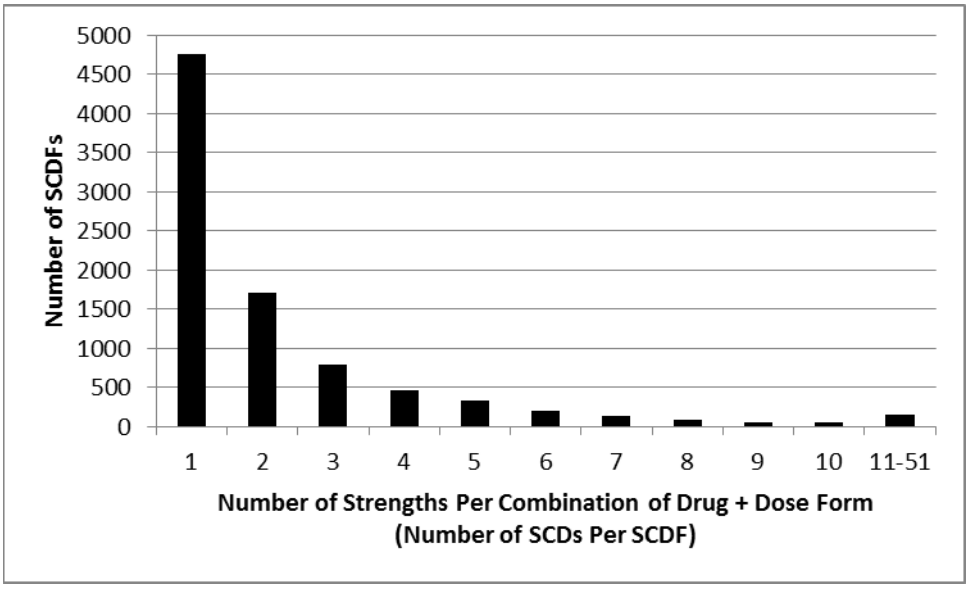

Figure 3: Relationship between SCDs and SCDFs. Most combinations of drug + dose form were mapped to a single SCDF but a small proportion of SCDFs represented many SCDs, indicating a large number of strengths available for the given combination of drug and dose form.

On the other end of the spectrum, 158 (1.8%) SCDFs were used by more than 10 SCDs each. The top 25 SCDFs (0.3%) were utilized by more than 20 SCDs each, representing 698 SCDs in total. The three most highly utilized SCDFs were "Menthol Lozenge" (RxCUI 374544), "Amylases / Endopeptidases / Lipase Enteric Coated Capsule" (RxCUI 402754), and "Guaifenesin / Phenylephrine Extended Release Tablet" (RxCUI 373391). The "menthol lozenge" SCDF was used by 51 SCDs that had strengths ranging from 1 mg to 18 mg. The "amylases/endopeptidases/lipase enteric coated capsule" SCDF was used by 45 SCDs that had varying combinations of strengths of the three ingredients. The "guaifenesin/phenylephrine extended release tablet" SCDF was used by 44 SCDs, distinguished not only by varying combinations of the two ingredients but also by different uses of the qualifier "12 HR". In fact, 24 of the 44 SCDs in this SCDF were identical pairs of drugs with the same strengths and dose form, but one specified "12 HR" and the other did not.

An ordered, concatenated list of ingredients was developed for each SCD. This list contained 8717 unique combinations of concatenated ingredients and dose form, which was expected based on the number of SCDFs. The list was grouped by ingredient(s) and the NDF-RT dose forms within each group were identified. Examples of the results are shown in **Table 6**. A total of 5021 unique combinations of ingredients were found.

Ingredient(s)	NDF-RT Dose Form(s)	NDF-RT Dose Form Type(s)
1-octacosanol	Oral Capsule	Orderable Drug Form
4-Aminobenzoate	Oral Capsule + Oral Tablet	Orderable Drug Form
4-Aminobenzoic Acid + Arginine	Topical Cream	Orderable Drug Form
Acetaminophen + Aspirin	Oral Powder + Oral Tablet	Orderable Drug Form
aclidinium	Dry Powder Inhaler	Drug Delivery Device
adalimumab	Injectable Solution + Prefilled Syringe	Drug Delivery Device + Orderable Drug Form

Table 6: NDF-RT Dose Forms, by Drug. The table lists examples of ingredient combinations and their respective related terms from NDF-RT Dose Form.

The type ("Drug Delivery Device" and/or "Orderable Drug Form") of dose form(s) available for each combination of ingredients was determined based on the NDF-RT hierarchy. The majority of ingredients (4702, 93.6% of the 5021 combinations) were related to one or more concepts from Orderable Drug Form only; these represented 15,776 SCDs. There were 47 (0.9%) ingredients representing 81 SCDs that were related to one or more concepts from Drug Delivery Device only. Interestingly, 272 (5.4%) ingredients were related to one or more concepts from both hierarchies, indicating inconsistency in how terms for dose form were related to a given drug. These cases represented 4411 SCDs, or 21.8% of the SCDs in this data set. Examples of drugs that were related to concepts from both hierarchies are shown in **Table 7**.

Ingredient(s)	NDF-RT Orderable Drug Form(s)	NDF-RT Drug Delivery Device(s)
ciclesonide	Inhalant Solution	Metered Dose Inhaler + Nasal Inhaler
Cromolyn	Inhalant Powder + Inhalant Solution + Nasal Solution + Nasal Spray + Ophthalmic Solution + Oral Capsule + Oral Solution	Metered Dose Inhaler + Nasal Inhaler
fluticasone	Inhalant Powder + Inhalant Solution + Topical Cream + Topical Lotion + Topical Ointment	Dry Powder Inhaler + Metered Dose Inhaler + Nasal Inhaler
heparin, porcine	Injectable Solution	Prefilled Syringe
Leuprolide	Injectable Solution + Injectable Suspension	Drug Implant + Prefilled Syringe

Table 7: NDF-RT Dose Forms, by Type and Drug. The table lists examples of drugs that were related to concepts from both NDF-RT Dose Form hierarchies.

Discussion

In this study we evaluated the potential ability of RxNorm to facilitate management of drug lists for CDS rules by providing standardized representations of generic drug name and route of administration. Generic drug name was clearly represented as ingredients. Anecdotal evidence suggested several different term types might contain information related to the route of administration. This study found route data in values of three attributes: RxNorm Dose Form, RxTerms route, and NDF-RT Dose Form. None of the value sets used by those attributes contained only route of administration, however, which presented a challenge when determining which to use to facilitate management of CDS rules.

The documentation for NDF-RT Dose Form indicates that the attribute is "initialized from RxNorm and is periodically resynchronized by computer algorithm" (11), which implies that some divergence may be anticipated over time. Nonetheless, we found this attribute to be identical to RxNorm Dose Form, with the caveat that some SCDs contained relationships to multiple terms from NDF-RT Dose Form. All but one of those related terms were outside the Dose Form hierarchy with similar spellings as the corresponding Dose Form term. This could suggest that those terms may have been introduced in error, a risk we recognized previously (24), and subsequently escaped the resynchronization process. The NUI codes for these terms are included in **Table 3** so they can be manually excluded from searches, if desired.

We found the content of the four term types was consistent between sources, although there was some variability in the semantic precoordination of concepts used by each attribute. In many cases the RxTerms new_dose_form attribute contained additional qualifiers that were not present in the other attributes, such as those which specified count (e.g., number of puffs for an inhaler), time-release (e.g., 12 HR), or volume (e.g., 1 ml). For example, the RxNorm/NDF-RT Dose Form "Prefilled Syringe" could not be mapped unambiguously to RxTerms new_dose_form, as the latter included a qualifier to indicate the volume of the syringe. In this case, there were 58 different values in RxTerms new_dose_form that map to "Prefilled Syringe", from "Prefilled Syringe 0.09 ml" to "Prefilled Syringe 125 ml". The inclusion of a volume metric within the term for dose form caused a significant expansion of the value set, which could complicate the management and use of these terms for CDS rules.

More than one quarter of the SCDs in the data set were missing relationships to RxTerms. The vast majority of them could be inferred, however, by using the RxTerms terms that were related to other SCDs that have the same value for RxNorm/NDF-RT Dose Form. Relationships for the remaining instances could not be assigned using this method largely due to ambiguity caused by count or volume qualifiers. In particular, most of those SCDs had a Dose Form of "prefilled syringe", which includes a specified volume in RxTerms. Without access to the algorithms used to assign RxTerms relationships, we could not ascertain the reason why so many relationships were missing from this data set. This may be partly due to the fact that RxTerms intentionally omits some drugs to improve query performance (10). Regardless, any query that uses terms from RxTerms as a parameter is likely to return incomplete results, which complicates or even prevents the use of RxTerms for the management of drug lists for CDS rules. We believe it would be better to define relationships for all drugs and allow implementers to filter the data set.

Our initial observations regarding injectable heparin suggested that the same drug could be classified as both an Orderable Drug Form and a Drug Delivery Device, based on the value of Dose Form. This study confirmed that observation and demonstrated that while this phenomenon affected a relatively small proportion of ingredients, those ingredients comprised nearly 22% of the SCDs in this data set. We were not able to find any documentation that describes the process by which relationships are assigned. Without a clear understanding of this process it would be difficult to confidently use those relationships for the management of drug lists used in CDS rules.

Finally, we observed extensive semantic precoordination of orthogonal concepts within the value sets used for each of the attributes in this study (RxNorm/NDF-RT Dose Form, RxTerms route, RxTerms new_dose_form). **Table 1** and **Table 2** illustrate terms that contain concepts for dose form, route, and/or drug delivery device, such as "oral tablet" and "topical cream". This precoordination complicates the computational use of these terms for managing drug lists and makes it difficult to use those terms appropriately.

Although RxNorm is intended to "assist with medication-related clinical decision support" (9), it was primarily developed as a standard for data exchange and semantic interoperability so it is not surprising that the data model may be more suited to this use case. In particular, the current structure and content for representing route of administration and dose form is not optimal for CDS. This is not unexpected, however, as the content and organization of biomedical ontologies may enable them to meet some use cases better than others (15, 25). As

RxNorm is adopted more widely it is likely that additional use cases will arise that will require extensions to the terminology.

Limitations

The limitations of this study include restrictions due to its scope. Specifically, we limited our evaluation to attributes that pertained to drug name and route of administration, and omitted analysis of RxNorm Dose Form Group (DFG) and Semantic Clinical Drug Form Group (SCDG). While it is possible these elements may be relevant to our use case, they are computational derivations of the attributes that were already included in the study. Similarly, we explored the hierarchy of NDF-RT Dose Form while evaluating semantic consistency but we did not investigate other classification schemes from that terminology. In particular, drug class would be relevant to drug-based CDS; this topic has been explored previously (24, 26, 27).

Finally, we intentionally scoped this evaluation to RxNorm, as it is a nationally-recognized standard that meets Meaningful Use requirements. Other terminologies with cross-references to RxNorm content might address some of the issues that were identified in this study. For example, the Drug Ontology (DrOn) is derived in part from RxNorm and follows formal ontological principles (28). It may be possible to extend RxNorm with data from other ontologies to meet the needs of our use case.

Conclusions

In this study we evaluated the potential ability of RxNorm to facilitate management of drug lists for CDS rules by providing standardized representations of generic drug name and route of administration. Generic drug names were clearly represented as ingredients. It was more difficult to find a robust representation for route of administration, however, and we explored several attributes to determine which might be most appropriate for our use case. None of those attributes provided an ideal, semantically "pure" form of route of administration.

In the course of these investigations we discovered several issues related to data quality, including erroneous or missing defined relationships, and the use of different concept hierarchies to represent the same drug. We also identified examples where the use of qualifier terms and the semantic precoordination of orthogonal concepts would complicate the use of the data.

This study demonstrates that while RxNorm is a valuable resource for the standardization of medications used in clinical practice, additional work is required to enhance the terminology so that it can support expanded use cases, such as managing drug lists for CDS. We encourage the NLM, content developers of drug knowledge bases, and the scientific community to continue to evaluate and collaboratively extend RxNorm for a variety of clinical uses.

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