A new route of administration hierarchy derived from dose forms supporting standardised drug dose calculations

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Background

Patient-level drug utilisation studies can provide crucial information for rational drug usage. These studies involve analysing data from various sources to gain insights into the patterns and determinants of medication use in real-world settings. Route of administration is one of these patterns, and another one is drug dose, which requires the knowledge of the route to correctly interpret records of drug products and their strength. Unfortunately, few observational databases provide route of administration records. Moreover, there are 365 different routes in the route domain in the current vocabulary, which, adopted from sources with different use cases in mind, proved insufficient to make clinically relevant categories for dose estimation and to our knowledge have largely been ignored in analytical use cases. The current system also provides no hierarchical relationships between different routes, which would be essential for creating summary reports and standardised dose calculations. The OMOP CDM and OHDSI vocabularies are a good foundation for attempting such standardisations, but previous attempts have not resulted in a consensus. DARWIN EU, whose majority of data partners are part of OHDSI are driving this work of building a hierarchical route of administration system that allows linking a drug's dose form to a route of administration and facilitates dose estimation.

Methods

We obtained all existing dose forms from ATHENA (searching for "Drug" domain, "dose form" concept class, “valid” flag and “RxNorm Extension” and “RxNorm” vocabularies). Based upon their name and looking at the actual drugs linked to them, we suggest a route for each dose form. TB (pharmacist) and AG (medical doctor) did this review independently and met for a consensus meeting with CR in which also the level, hierarchies, categories, and names of routes were defined. Dose forms including systemic and local administration were subject to more thorough scrutiny for whom the decision was based upon the importance of the individual ingredients and to avoid misclassification in (systemic) dose estimation.

We further estimated the frequency and proportion of the individual drug concept ids per newly suggested route from the drug strength table of both CPRD GOLD and CPRD AURUM.

Results

We yielded 214 dose forms in ATHENA. We created a route of administration hierarchy with "systemic", "local", "other" (undefinable through dose form), and “has no dose form” as top classifiers. Subclassifications and their hierarchy are shown in Figure 1.

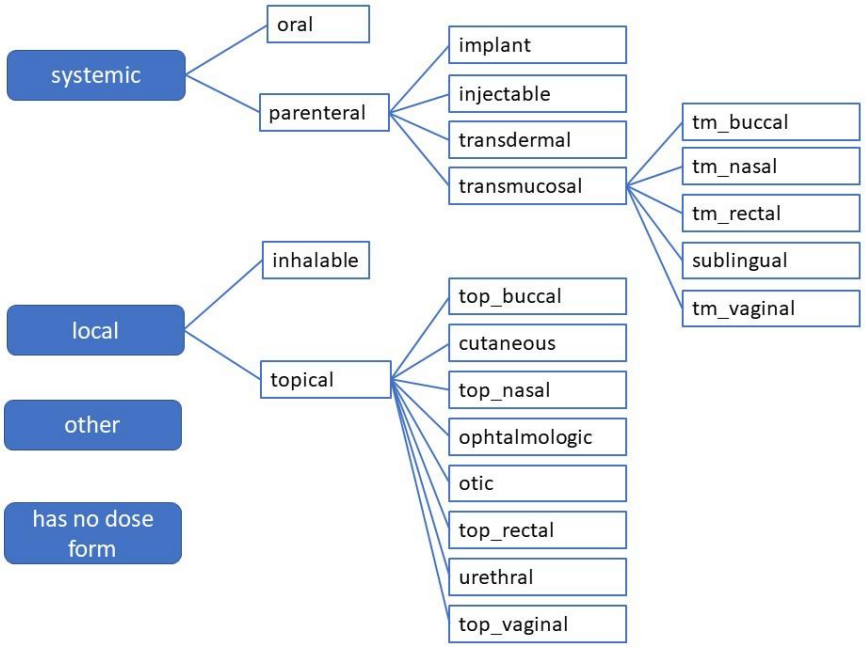

Figure 1. Suggested names and hierarchy of new route vocabulary.

Most dose forms can be unambiguously assigned to a route of administration, but there are exceptions where we had to make a choice. Our review had a focus on systemic administrations because they are more relevant for dose estimations – topical administration faces surface tissue and dosing is therefore less stringent. Therefore, we decided to classify dose forms like “mucosal spray”, “oral gel” or “nasal powder” as systemic to not miss important use cases such as nitroglycerin, carbidopa, and sumatriptan. Yet, we categorised the dose form “topical gel” into the route category “topical cutaneous” although there was transdermal estradiol among them. We did this because the majority of applications were cutaneous, and we did not want to misclassify topical anti-inflammatory agents into the systemic category.

Some examples are listed in Table 1, where we can see the new route categorisation per dose form.

Table 1. Examples of suggested categorisation among the 214 existing dose form

Dose form concept id	**Dose form concept name**	**Assigned route**
19103220	12 hour Extended Release Capsule	oral
19124968	Drug Implant	implant
46234466	Auto-Injector	injectable
1856271	Intrauterine System	parenteral
19082049	16 Hour Transdermal Patch	transdermal
40164192	Buccal Film	tm_buccal
35604877	Nasal Powder	tm_nasal
19082627	Enema	tm_rectal
40220762	Sublingual Powder	sublingual
19082230	Vaginal Powder	tm_vaginal
19127579	Dry Powder Inhaler	inhalable
19110977	Cream	topical
19095918	Oral Paste	top_buccal

19135446	Augmented Topical Gel	cutaneous
43563498	Nasal Pin	top_nasal
779945	Drug-Eluting Contact Lens	ophtalmologic
19082194	Otic Ointment	otic
19082574	Rectal Foam	top_rectal
19082575	Urethral Suppository	urethral
21014179	Vaginal delivery system	top_vaginal
19082653	Bar	other

The frequency and proportion of unique drug concept ids per newly suggested routes in CPRD GOLD and CPRD AURUM are depicted in Table 2.

Table 2. Number of unique drug concept ids in the drug strength table of CPRD GOLD and CPRD AURUM that would be linked to the newly suggested route

	CPRD GOLD unique drug concept ids, n (%)	**CPRD AURUM unique drug concept ids, n (%)**
oral	906’064 (48.9%)	929’935 (48.7%)
injectable	365’685 (19.7%)	378’184 (19.8%)
has no dose form	261’108 (14.1%)	272’888 (14.3%)
cutaneous	171’165 (9.2%)	174’156 (9.1%)
ophtalmologic	42’344 (2.3%)	43’260 (2.3%)
inhalable	28’121 (1.5%)	29’297 (1.5%)
transdermal	13’752 (0.7%)	14’050 (0.7%)
top_vaginal	11’917 (0.6%)	12’258 (0.6%)
tm_rectal	11’500 (0.6%)	11’757 (0.6%)
tm_nasal	11’372 (0.6%)	11’620 (0.6%)
tm_buccal	10’101 (0.5%)	10’642 (0.6%)
top_rectal	3120 (0.2%)	3354 (0.2%)
topical	3112 (0.2%)	3213 (0.2%)
other	2620 (0.1%)	2668 (0.1%)
otic	2367 (0.1%)	2470 (0.1%)
sublingual	2236 (0.1%)	2310 (0.1%)
top_buccal	2190 (0.1%)	2203 (0.1%)
top_nasal	1622 (0.1%)	1626 (0.1%)
implant	1300 (0.1%)	1384 (0.1%)
urethral	437 (0%)	437 (0%)
tm_vaginal	6 (0%)	6 (0%)

Conclusion

We believe this new route of administration hierarchy, derived from and linked to dose forms of drugs will enable the use of route information in standardised analytics. This has value per se and is instrumental for dose calculations, which have been largely omitted to date because of the complexity of how to correctly interpret the strengths of a drug. The use of dose form groups (n = 47) are still many and do not yield the same level of clinical relevance as our newly suggested route of administration.