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Analysis of Concomitant Medication Data

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ABSTRACT

Concomitant medication (in parlance, conmeds) collection is mandated by GCP for clinical trials. However, conmeds are frequently unanalyzed. Well-analyzed conmeds can indicate which adverse events and first-line medications are linked to the experimental medication and which medications may interact. The integrated summary of safety (ISS) provides an opportunity to perform a good concomitant medication analysis before the approval process is complete and in time for label writing.

Any concomitant medication analysis must consider all trial subjects exposed to both experimental medication and the placebo. Analyzing the placebo exposed subjects provides information about a baseline level of concomitant medications. Any category of medications which exceeds a pre-determined threshold, often 5% of the safety population, is reported.

In CDISC, concomitant medication data is reported in the CM domain. Analysis can be accomplished straight from this raw data or when merged with MH, AE, EX, SU, DM or ADSL data into an ADaM dataset. Adverse events are reported and grouped with the contemporary version of MedDRA. Conmeds are normally reported and grouped by ATC code level.

The ideal concomitant medication analysis would identify 1) all medications (or medication classes) which are reported for greater than a threshold level (5%), 2) all medications where the difference between placebo and experimental is greater than a threshold level (1%) 3) all medications with a significant difference in the distribution of adverse events between the two groups and 4) all medications which differ by a threshold level (10%) between significant outcome categories (e.g. early withdraws, SAE, successful treatment.)

INTRODUCTION: WHY DO A CONCOMITANT MEDICATION ANALYSIS?

The subjects in clinical trials are human beings and as such normally act rationally and with reason. Almost every reported concomitant medication has a reason and most of these reasons should be reported as adverse event. A pattern of adverse events may become a side effect or a warning sign of rare but significant other issues. Concomitant medications may also indicate a patient status, like hypertension, asthma or arthritis which affects the pharmacokinetics or pharmacodynamics of the study drug. In addition, the earliest indication of a serious adverse event may have been self-treated with an OTC concomitant medication; an understanding of how frequent that OTC is employed by the entire study population will provide perspective to that analysis.

Although nothing but the most casual review of concomitant medications is required for every clinical trial (would you notice and report if every treated subject reported taking antacids and no placebo exposed subjects did?) there is a natural point where a thorough concomitant medication analysis is appropriate, in the ISS (integrated summary of safety)or the annual update. Summarizing 1,000 subjects exposed to active treatment should provide a glimmer of information about any factor important enough to study before the product proceeds to approval submission. The purpose of this analysis should never be perceived as the key piece of evidence identifying an unsafe compound. Instead, it may be a supporting piece of evidence, indicative of a pattern for further consideration. A good concomitant medication analysis will point the way toward issues which will either be considered for contraindication, for inclusion within the label, or for further investigation in Phase IV studies.

ORGANIZATION SDTM OR ADAM

Conmeds have their own domain in SDTM, specifically CM; a standard intervention domain. While the variables are largely standard and straight-forward in definition and usage, we normally employ an existing variable in the CM domain to speed analysis, specifically, CMCLASCD to store the ATC code. The ATC is the Anatomical Therapeutic

Chemical Classification System code, an international code system compiled by the WHO; every prescription medication and nearly every OTC medication has at least one (and occasionally more) unique ATC code. Multiple codes are generated for principle usages of the same medication. Of aspirin's three ATC codes, the first is A01AD05. This breaks into five separate codes each with a non-varying format. The first character, /A/ here is for which of fourteen body systems, in this case alimentary system. The /01/ is stomalogical preparations. The second /A/, the /D/ and the /05/ complete the unique coding for aspirin. Aspirin's other codes are B01AC06 (as a platelet inhibitor) and N02BA01 (for its analgesic, that is anti-pain, usage), and demonstrate that the pattern of the coding does not vary. Thus, we include one entire ATC code in CMCLASCD.

Most implementations of ADaM do not have a database which is a direct descendent of SDTM.CM. If the sponsor requires that all analysis and reporting be accomplished based on ADaM domains then the creation of an ADCM dataset is quite straightforward. We simply move over the CMCLASCD variable, normally using a name which explicitly identifies the contents as the ATC code, as well as subject identifier, timing and dosage, particularly summary dosage. These can be standardized by the application of DDDs (defined daily dosages) which is also a WHO standard maintained for each medication. There are a few classes of medication in which access to the ADSL to determine age and gender may be required to correctly standardize the DDD. If possible, we will also retain any indication information which is gathered, although most data management departments simply throw this data away.

ANALYSIS

The first analysis is conducted on conmeds before even speaking to the statistician, pharmacovigilance or clinical people. However, keep it very simple. Employing the first three characters of ATC code variable and a large format, which is saved for re-use, produces simple report which provides a count of events, days on events and unique subjects in each of the fourteen first letter codes and the present sub-codes, broken by treatment group.

Table Sample

	All Dosings		Count of Days Dosed		Unique Subjects	
	Trt A	Placebo	Trt A	Placebo	Trt A	Placebo
A (Alimentary)	501	399	2047	2001	298	272
A01 (Stomological)	440	287	1554	1409	201	196
A02 (Acid Dis)	21	12	177	152	11	6
. . .						
B (Blood)	47	60	301	376	27	33
B01 (Antithrombotics)	4	8	20	38	3	5
. . .						

Table 1. Concomitant Medications

Obviously, spacing has forced abbreviation here. There is a very similar adverse events (AE) table, from which we can borrow the majority of the code for this table, and then can now approach a variety of people with different areas of analysis expertise and ask them two simple questions. First, is further analysis required; does any of these categories merit further investigation? Second, if so, what criteria should be implemented as worthy of interest? That is, how large a difference between treatment categories merits further analysis?

Within the A (Alimentary) grouping the 501 dosings for the Treatment A group compared to the 399 for the placebo group appear slightly elevated (a 25% increase) but the unique subjects and count of days dosed both mitigate likely interest. However, this is a judgment which I allow the statistician, pharmacovigilance specialist, the clinical scientist and anyone else who reviews this table to make. If this table was destined for outside the company, there are

improvements required. First, medications with multiple codes are re-listed with all of their codes. When a subject takes aspirin to relieve a toothache, it still inhibits platelet action. We have a small list of ATC codes with multiples which is sent to both the statistician approving the table and the validating programmer. Note that assuming all codes could be bypassed if data managers faithfully reported the indication and linked it to the proper ATC code. No one known has met such a data manager.

For whatever choice of categories is communicated, a table is prepared similar to the above Table 1 with the chosen categories exploded out to the third, fourth or even fifth code level as directed. That is, for aspirin's A01AD05 code, if directed to target the A01 code one can present: a) the A01 category, b) the A01A category (and all other A01X categories), c) the A01AD category (again with all A01XX categories) and even d) the A01AD05 reports. We recycle the code for Table 1 (q.v.) and generate a specific format for the labels. Again, we make the format available to my verification programmer, as there is no sense in two people typing in the same list.

Normally, a small number of categories need specific reporting. For example, N02 which includes NSAIDs, typically the largest single category, or R06, antihistamines which are seasonally important in many trials are frequently requested. For many trials there are specific areas important because of their indication, thus for a trial on a high-blood pressure medication, prescriptions for eye care may be of special interest.

Table Sample

	All Dosings		Count of Days Dosed		Unique Subjects	
	Trt A	Placebo	Trt A	Placebo	Trt A	Placebo
C08 (CA channel blockers)	47	60	200	68	23	26
C08C (CCB-vascular)	4	0	120	0	2	0
C08D (CCB-cardio)	40	59	20	38	19	25
C08E (CCB-n-select)	3	0	60	0	2	0
C08G (CCB-diuretics)	0	1	0	30	0	1
N02 (Analgesics)	554	420	1999	1837	303	291
N02A (Opiods)	1	0	14	0	1	0
N02B (Other)	441	289	1559	1418	213	201
N02C (Anti-Migraine)	102	131	422	419	89	90
. . .						

Table 2 (NSAIDs, N02 and calcium channel blockers, C08)

If desired any row below a pre-specified threshold value may be optionally deleted. After providing this level of information, we frequently find additional requests to provide a list of which individuals took specific medications or classes of medications. This also generates requests for patient profiles to examine the context of the concomitant

medication. Both of these may be informally produced for analysis and later be requested formally to be included in communication with a regulatory agency. Macros for both are widely available <Hantsch & Stuelpner, 2012.>

CONCLUSIONS

A wise man once described the science side of the typical pharmaceutical company as twelve teams of analysts who all examine the different stages of the clinical trial data stream in unique ways and want the data displayed in their own way, which they believe is the only logical way to present the data. Meanwhile, the clinical trial data stream team has a dozen individuals who believe their task is the most important portion of preparing the data for the twelve analysts. The twelve analysts want their data as soon as possible and yet the twelve data stream people keep prodding the earlier individuals to deliver earlier so that they can spend as much time as possible improving the data.

A good concomitant medication (conmed) analysis may not fall directly into any of these 24 camps and in the rush to complete the required tasks often is overlooked. However, this paper has shown how to adapt an already existing code set quickly and easily to develop a preliminary table which will give several variants of analyst valuable information to consider before they commence their regular analysis. It has also shown how a secondary table may be created to provide more focused and detailed information responding to analyst requests.

REFERENCES

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