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# Beyond WHODrug: Insight into Concomitant Medication Data Analysis

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## ABSTRACT

Concomitant medication (con-med) is not just about WHODrug B3/C3 coding. ICH guidance requires sponsors to collect con-med. It is important to assess its impact on participant safety, drug-related adverse events, confounding, or additive effects on efficacy endpoints.

Con-med can have a study-defining impact on estimands. For example, systemic anti-cancer therapy is considered an intercurrent event under the ICH E9(R1)[4] addendum. It affects the treatment effect on disease progression. In cardiovascular trials, both baseline and on-treatment diuretic dose increase can affect treatment effects in heart failure participants. This paper will share the PHUSE con-med data collection standard, use an example to suggest how to avoid collecting unreliable and dirty data, demonstrate how the SDTM data standard connects concomitant medication with medical history and adverse events, present the ADCM standard for common statistical analysis, and share a pragmatic method for deriving the average daily dose to model study-specific concomitant medication.

## INTRODUCTION

Concomitant medications (con-meds) are any prescription or non-prescription medications (i.e., over-the-counter drugs and dietary supplements) a patient may be taking in addition to the investigational drug product(s). All clinical trials must collect the concomitant medication name, dose, etiology, start, and end dates in all trials. Both ICH and FDA have relevant guidance on the con-meds. Properly collecting and analyzing concomitant medication is critical for safety and efficacy analysis and trial compliance.

## WHODrug AND GUIDANCE ON CONCOMITANT MEDICATION

On December 16, 2025, FDA issued the updated SDTCG v6.1[1] for regulatory submission:

1. CMDECOD should be populated with the active substances from the WHODrug Global Dictionary[2].
2. --CLAS is recommended to be populated with the Anatomic Therapeutic Chemical (ATC) class (and --CLASCD with class code) most suitable per intended use.
3. Populating CMCLAS or ATC Class with "Multiple" is not useful. All Anatomic Therapeutic Chemical (ATC) classes and CMCLASCD are expected. If there are additional ATC classes, then flag the row in the main dataset and include the additional ATC classes in SUPPCM or FACM domains.
4. ATC classes and codes should be submitted at the fourth level or most specific available as defined within WHODrug Global.
5. There is no requirement to re-code earlier studies to align with the WHODrug Global version of later studies. However, the conmed dataset for pooled data, e.g., ISS, should include WHODrug Global terms from one accepted current version (not a mixture of versions).

### WHODrug GLOBAL DICTIONARY

Since FDA and other health authorities such as EMA, PDMA and NMPA accept WHODrug ATC classification as the standard for regulatory submission and safety monitoring. WHODrug GLOBAL dictionary became the SDTM standard terminology for medication coding. The commonly used classification for con-med summary table is by ATC level 2 or 4 and preferred name (CMDECOD). ATC stands for Anatomical Therapeutic Chemical classification system.

**Table 1. Illustration ATC Classification and Five ATC Levels for Diuretics Furosemide**

| ATC Class (ATCy) | ATC Code (ATCyCD) |
|---|---|
| 1st level (1 letter): Anatomical main group | C (Cardiovascular system) |
| 2nd level (2 digits): Therapeutic subgroup | C03 (Diuretics) |
| 3rd level (1 letter): Pharmacological subgroup | C03C (High-ceiling diuretics, loop diuretics) |
| 4th level (1 letter): Chemical subgroup | C03CA: Sulfonamides, plain (loop diuretics subgroup) |
| 5th level (2 digits): Chemical substance (specific active ingredient) | C03CA01: Furosemide |

## ADAM OCCURRENCE DATA STRUCTURE FOR CONCOMITANT MEDICATION ANALYSIS

The concomitant medication analysis data ADCM fits ADaM Occurrence Data Structure (OCCDS)[3]. To meet the FDA submission requirement, sponsors should, at a minimum, include the variables presented in table 2 in ADCM.

| Variable Name | Variable Label | Type | Codelist/ Controlled Terms | Core | CDISC Notes |
|---|---|---|---|---|---|
| CMTRT | Reported Name of Drug, Med, or Therapy | Char | | Req | CM.CMTRT |
| CMDECOD | Standardized Medication Name | Char | WHODRUG | Cond | CM.CMDECOD |
| CMCLAS | Medication Class | Char | WHODRUG | Perm | CM.CMCLAS<br>Include the dictionary version in the metadata. |
| CMCLASCD | Medication Class Code | Char | WHODRUG | Perm | CM.CMCLASCD<br>Include the dictionary version in the metadata. |
| ATCy | ATC Level y Text | Char | WHODRUG | Cond | SUPPCM.QVAL where QNAM="ATCy"<br><br>*y = 1 to (4 or 5 ) |
| ATCyCD | ATC Level y Code | Char | WHODRUG | Cond | SUPPCM.QVAL where QNAM="ATCyCD"<br><br>*y = 1 to (4 or 5) |

| Variable Name | Variable Label | Type | Codelist/ Controlled Terms | Core | CDISC Notes |
|---|---|---|---|---|---|
| ACATy | Analysis Category y | Char | | Perm | Category used in analysis. May be derived from --CAT and/or --SCAT. Examples include records of special interest like prohibited medications, concomitant medications taken during an infusion reaction, growth factors, antimicrobial medications, and other such categories not defined elsewhere or present in SDTM domains. |

## CONCOMITANT MEDICATION AS INCURRENT EVENTS

ICH E9(R1)[4] is an addendum to the original ICH E9 guidance (Statistical Principles for Clinical Trials). It introduced and mandated the use of the estimands (treatment effect) framework in clinical trial planning, conduct, analysis, and reporting. Estimand is a precise description of exactly what you want (or demand) to find out, which includes population, endpoint, how to handle intercurrent events and summary of the variable of interest.

The use of rescue medication, death, start of other therapies are all intercurrent events that study protocol or SAP should address its impact on estimands.

**Intercurrent events are defined as**: "*events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest*".

Therefore, it is necessary to incorporate strategies to address each type of intercurrent events such as treatment discontinuation, use of rescue medication, death, start of other therapies when describing the clinical question of interest and precisely defining the estimands.

**Table 3. ADCM Example: Post-treatment Anti-cancer Therapies for Subject 100-001**

(Note: The table is split after the first four columns)

| Subject | CMTRT | CMDECOD | ACT1CD (ATC1) |
|---|---|---|---|
| 001 | AB-101 | NATURAL KILLER CELLS | L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS; ANTINEOPLASTIC AGENTS) |
| 001 | ABEMACICLIB | ABEMACICLIB | L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS) |
| 001 | ACALABRUTINIB | ACALABRUTINIB | L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS) |
| 002 | ALLOGENIC STEM CELL TRANSPLANT | ALLOGENIC STEM CELLS NOS | V (VARIOUS) |
| 002 | THYMOGLOBULIN | ANTITHYMOCYTE IMMUNOGLOBULIN (RABBIT) | L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS) |
| 002 | ARSENIC TRIOXIDE | ARSENIC TRIOXIDE | L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS) |

| Subject | ACT2CD (ATC2) | ACT3CD (ATC3) | ACT4CD (ATC4) | ACAT1 |
|---|---|---|---|---|
| 001 | L01 (ANTINEOPLASTIC AGENTS) | L01X (OTHER ANTINEOPLASTIC AGENTS) | L01XL (ANTINEOPLASTIC CELL AND GENE THERAPY) | Systemic Anti-cancer Therapy |
| 001 | L01 (ANTINEOPLASTIC AGENTS) | L01E (PROTEIN KINASE INHIBITORS) | L01EF (CYCLIN-DEPENDENT KINASE (CDK) INHIBITORS) | Systemic Anti-cancer Therapy |
| 001 | L01 (ANTINEOPLASTIC AGENTS) | L01E (PROTEIN KINASE INHIBITORS) | L01EL (BRUTON'S TYROSINE KINASE (BTK) INHIBITORS) | Systemic Anti-cancer Therapy |
| 002 | V03 (ALL OTHER THERAPEUTIC PRODUCTS) | V03A (ALL OTHER THERAPEUTIC PRODUCTS) | V03AX （OTHER THERAPEUTIC PRODUCTS） | Systemic Anti-cancer Therapy |
| 002 | L04 (IMMUNOSUPPRESSANTS) | L04A (IMMUNOSUPPRESSANTS) | L04AA (SELECTIVE IMMUNOSUPPRESSANTS） | Systemic Anti-cancer Therapy: Prohibited Medication |
| 002 | L01(ANTINEOPLASTIC AGENTS) | L01X (OTHER ANTINEOPLASTIC AGENTS) | L01XX (OTHER ANTINEOPLASTIC AGENTS) | Systemic Anti-cancer Therapy |

For oncology study, subject taking additional anti-cancer therapy while on study drug indicates disease deterioration. In **Table 3**, ACAT1 indicates that these medications are systemic anti-cancer therapies, and thymoglobulin is a prohibited medication as specified per protocol. Per ICH E9(R1), this is an intercurrent event. The impacts on estimands are:

- Responses after initiation of anti-cancer therapy can confound the treatment effect of the investigational drug. The protocol and statistical analysis plan (SAP) may specify censoring the progression-free survival (PFS) and response at the last response assessment prior to the first systemic anti-cancer therapy. A sensitivity analysis can be specified to estimate the treatment effect on PFS without censoring at the first post-treatment systemic anti-cancer therapy.
- Protocols may specify prohibited medication as a critical protocol deviation leading to treatment discontinuation if it affects endpoints. The PHUSE working group developed a data collection standard[5] to implement the ICH E9(R1) estimand framework. They created very detailed categories to collect different events under treatment discontinuation, as shown in **Table 4**. Reasons for treatment discontinuation are explicitly listed under the bolded categories. Protocol deviation and logistical problems are separated, and each has granular subcategories. WITHDRAWAL BY PARTICIPANT and PHYSICIAN DECISION were removed from the list and replaced with actual situations under LOGISTICAL PROBLEM.

**Table 4. End of Treatment Discontinuation**

| | |
|---|---|
| What was the participant's status?<br>**DS.DSDECOD**<br>**DS.DSTERM** | • **COMPLETED**<br>• **ADVERSE EVENT. LINK TO ADVERSE EVENT: _____**<br>• **APPROVED DRUG AVAILABLE FOR INDICATION**<br>• **DEATH**<br>• **LACK OF EFFICACY** |

| | |
|---|---|
| | • **LOGISTICAL PROBLEM**<br>o CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE<br>o DIFFICULTY TRAVELING TO SITE<br>o GEOPOLITICAL LOGISTICAL RESTRICTIONS<br>o OPERATIONAL ERROR<br>o PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY INTERVENTION<br>o RELOCATION<br>o SCHEDULE CONFLICTS<br>o STUDY TERMINATION OR SITE CLOSURE<br>o UNSATISFIED WITH STUDY PROCEDURES<br>• **LOST TO FOLLOW-UP**<br>• **PREGNANCY**<br>• **PROGRESSIVE DISEASE**<br>• **PROTOCOL DEVIATION**<br>o DID NOT MEET STUDY ELIGIBILITY CRITERIA AT ENROLLMENT<br>o NONCOMPLIANCE TO STUDY INTERVENTION<br>o NONCOMPLIANCE TO STUDY PROCEDURES<br>o TOOK PROTOCOL-PROHIBITED CONCOMITANT MEDICATIONS<br>• **SUFFICIENT EFFICACY**<br>• **TREATMENT EXPERIENCE CONCERNS**<br>o FEAR OF NEW OR RECURRENT ADVERSE EVENTS<br>o UNSATISFIED WITH STUDY DRUG DELIVERY DEVICES/METHODS |

## CAN WE USE CMCLAS IN CON-MED SUMMARY TABLE

A specific drug name can be associated with multiple ATC codes. This is often due to possible use for several indications. CMCLAS and CMCLASCD can therefore be displayed as 'Multiple' (CMIND='ADVERSE EVENT'), while the multiple ATC codes are mapped to SUPPCM. The table below shows the relationship.

**Table 4. Value of CMCLAS/CMCLASCD as 'Multiple'**

| USUBJID | CMSPID | CMTRT | CMDECOD | CMCLAS | CMCLASCD |
|---|---|---|---|---|---|
| 100-001 | 25181-25195CM000000002298 | CORTISONE | CORTISONE | MULTIPLE | MULTIPLE |

**SUPPCM:**

| IDVAR | IDVARVAL | QNAME | QLABEL | QVAL |
|---|---|---|---|---|
| CMSPID | 25181-25195CM000000002298 | CMCLAS01 | Medication Class 1 | GLUCOCORTICOIDS |
| CMSPID | 25181-25195CM000000002298 | CMCLAS02 | Medication Class 2 | CORTICOSTEROIDS, PLAIN |

| IDVAR | IDVARVAL | QNAME | QLABEL | QVAL |
|---|---|---|---|---|
| CMSPID | 25181-25195CM000000002298 | CMCLAS03 | Medication Class 3 | HOMEOPATHIC PREPARATION |
| CMSPID | 25181-25195CM000000002298 | CMCLCD01 | Medication Class Code 1 | H02AB |
| CMSPID | 25181-25195CM000000002298 | CMCLCD02 | Medication Class Code 2 | S01BA |
| CMSPID | 25181-25195CM000000002298 | CMCLCD03 | Medication Class Code 3 | V91 |

The protocol or SAP may specify that the conmed summary is by ATC level 2 or 4 and preferred term. Since "Multiple" does not provide a precise medication class, it would be more appropriate to use ATC level 2 or ATC level 4 rather than CMCLAS in the summary table. This categorizes conmeds clearly and meets FDA requirements.

## STATISTICAL ANALYSIS ABOUT CONCOMITANT MEDICATION

### THE MOST COMMON ANALYSIS: SUMMARY BY ACT CLASS AND PREFERRED TERM

The mock summary of ACT level 2 or 4 by medication preferred term requires flags in ADCM. If the analysis is for sub-categories summary such as systemic anti-therapies and immunosuppressant. It is not efficient to create too many sets of these indicator variables as it is hard to track and prone to error.

| Variable Name | Variable Label | Type | Core | CDISC Notes |
|---|---|---|---|---|
| AOCCFL | 1st Occurrence within Subject Flag | Char | Perm | Character indicator for the first occurrence of any event/intervention/finding within the subject. |
| AOCCPFL | 1st Occurrence of Preferred Term Flag | Char | Perm | Character indicator for the first occurrence of the preferred term within the subject. |
| AOCCSFL | 1st Occurrence of SOC Flag | Char | Perm | Character indicator for the first occurrence of the system organ class within the subject. |

| Summary of Concomitant Medication | | | |
|---|---|---|---|
| **ATC Level 2/ Preferred Name (or ATC Level 4)** **AOCCFL** | **Treaatment A (N=xx) n (%)** | **Treatment B (N=xx) n (%)** | **Total (N=xx) n (%)** |
| Participants Reporting At Least One Concomitant Medication | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | | | |
| ATC Classification 2 or 4 **AOCCSFL** | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Medication Preferred Name **CMDECOD** **AOCCPFL** | xx (xx.x) | xx (xx.x) | xx (xx.x) |

### CHECK STANDARD CARE MEDICATION ON TITRIATION

In cardiovascular trials, diuretics are primarily maintenance drugs for heart failure to manage chronic fluid retention, but they are also used as emergency treatments to relieve acute congestion (pulmonary edema). Participants are normally allowed to take them while on the study drug. The titration analysis reflects disease condition for both safety and efficacy analysis. Dose intensification can be defined as one of the criteria for composite cardiovascular events. If this is important to the interpretation of the trial, then it trial should accurately collect information on the dose and dose frequency to be able to calculate total daily doses (alternatively, only the total daily dose may be collected).

1. Participants can take different forms of diuretics. The dose needs to be standardized to a furosemide-equivalent daily dose based on dose frequency.
2. Derive furosemide-equivalent daily dose:
   - Torasemide dose x 2 equals the furosemide-equivalent dose.
   - Dose frequency is often missing. This can sometimes be addressed by checking for double entries with different dosing on the same day. It is preferable to implement CDISC terminology in the EDC to avoid inconsistent data values for frequency and route.
3. Check dose increase from baseline (CMSEQ=1) for titration
4. Count total number of titrations from baseline.

The above derivation serves input data for statistical modeling. We can predict cardiovascular events using the number of titrations at baseline and/or from first dose to the end of treatment.

| SUBJID | CMSEQ | CMDECOD | ATC4 | ASTDT | AENDT | TRTSDT |
|---|---|---|---|---|---|---|
| 100-001 | 1 | TORASEMIDE | SULFONAMIDES, PLAIN | 19Apr2023 | 21Dec2023 | 20Nov2023 |
| 100-001 | 2 | TORASEMIDE | SULFONAMIDES, PLAIN | 21Dec2023 | 17May2024 | 20Nov2023 |
| 100-001 | 3 | TORASEMIDE | SULFONAMIDES, PLAIN | 18May2024 | 09Jul2024 | 20Nov2023 |
| 100-001 | 4 | TORASEMIDE | SULFONAMIDES, PLAIN | 19Jul2024 | 05Dec2024 | 20Nov2023 |
| 100-001 | 5 | TORASEMIDE | SULFONAMIDES, PLAIN | 06Dec2024 | 11Feb2025 | 20Nov2023 |

| CMSEQ | CMDOSE | CMDOSFRQ | Other Frequency | Furosemide Eqv. Dose | Titration from Baseline |
|---|---|---|---|---|---|
| 1 | 15 | | 10mg (morning) - 5mg (midday) - 0mg (evening) | 30 | |
| 2 | 30 | QD | | 60 | Y |
| 3 | 40 | | 20mg (morning) - 20mg (midday) - 0mg (Evening) | 80 | Y |
| 4 | 30 | | 20mg (morning) -10mg (midday) -0 (evening) | 60 | |
| 5 | 40 | | 20 mg - 20 mg - 0- 0 | 80 | Y |

## CONCOMITANT DATA COLLECTION:

PHUSE working group created the following concomitant medication form[5]. Any medication used for adverse events, clinical events or medical history can be linked to the recorded event via a link ID. This helps in assessing whether toxicity was from the study drug or was contributed by the standard of care.

| | | |
|---|---|---|
| Indicate if the participant took any concomitant medication/ treatment. | Were any concomitant medications taken?<br>**Not submitted** | • Yes<br>• No |
| Record only one treatment per line. Provide the full trade name of the medication/ treatment | What was the medication?<br>**CM.CMTRT** | |

| | | |
|---|---|---|
| Record the specific indication for which the medication was taken. | For what indication was the medication taken?<br>**CM.CMINDC**<br>**SUPPCM.QVAL where SUPPCM.QNAM = "AELINK" and SUPPCM.QLABEL = "Related Adverse Event"**<br>**SUPPCM.QVAL where SUPPCM.QNAM = "CELINK" and SUPPCM.QLABEL = "Related Clinical Event"**<br>**SUPPCM.QVAL where SUPPCM.QNAM = "MHLINK" and SUPPCM.QLABEL = "Related Medical History"** | • ADVERSE EVENT. LINK TO ADVERSE EVENT: ____<br>• CLINICAL EVENT. LINK TO CLINICAL EVENT: ___<br>• MEDICAL HISTORY. LINK TO MEDICAL HISTORY: ___ |
| Record the specific reason why the medication was taken | For what reason was the medication taken?<br>**SUPPCM.QVAL where SUPPCM.QNAM = "CMREAS" and SUPPCM. QLABEL = "Reason"** | • NON-THERAPEUTIC USE<br>• PROPHYLAXIS FOR <xxx><br>• REQUIRED CONCOMITANT MEDICATION FOR THE STUDY<br>• VACCINATIONS<br>• <STUDY INDICATION> |
| | Start Date<br>**CM.CMSTDTC** | |
| | Is the medication ongoing?<br>**CM.CMENRF or CMENRTPT** | • Yes |
| | End Date<br>**CM.CMENDTC** | |

## CONCLUSION

The use of prohibited medication as an intercurrent event is a confounding factor on treatment effects in oncology studies. The study protocol needs to address strategies within the estimands framework. ADCM should, at a minimum, include the fourth ATC level and corresponding codes to comply with the FDA SDTCG guidance. To summarize conmeds, ATC level 2 or 4 and preferred terms are commonly used in the summary table. Since CMCLAS can be "Multiple," which has no precise classification, it should not be used in the conmed summary table. Properly linking conmeds to adverse events or medical history in the EDC and SDTM can provide detailed information for safety analysis. For EDC conmed frequency collection, CDISC terminology should be used, and free-text fields should be avoided to ensure more accurate total daily dose data for analysis.

## REFERNCES


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