Analyses and Displays Associated with Demographics, Disposition, and Medications

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1. Introduction: Purpose of this Document

This white paper provides advice on displaying, summarizing, and/or analyzing demographics, disposition, and medication (prior and concomitant therapy) in the tables, figures, and listings (TFLs) of Phase 2-4 clinical trials and integrated summary documents. This white paper also provides advice on collection, if a particular recommended display requires data to be collected in a certain manner that may differ from current practice. The intent is to begin the process of developing a common standard for analysis and reporting of collected information that is used across clinical trials and across therapeutic areas. Separate white papers provide recommended TFLs for other data commonly collected across therapeutic areas (e.g., adverse events, laboratory measurements, vital signs, electrocardiograms, and pharmacokinetics) and can be found in the Pharmaceuticals User Software Exchange (PHUSE) Computational Science Final Deliverables Catalog [1].

The development of standard TFLs and associated analyses will lead to improved standardization of data from collection through data display and analysis. The development of standard TFLs will also lead to improved and harmonized product lifecycle management across therapeutic areas by ensuring that reviewers receive clinically relevant and meaningful summary data of subject characteristics and analyses of subject safety for benefit-risk assessment. As with any standard output, the value proposition of standards for TFLs is to answer the common questions associated with demographics, disposition, and medications in a commonly accepted manner. There is value in the familiarity of commonly constructed TFLs for those creating the TFLs and those using the TFLs to interpret data. Standard outputs make more efficient use of resources. Use of standard outputs also allows for easier aggregation of data across the compound. This white paper reflects recommendations that would lead to more consistent TFLs, but the recommendations should not be interpreted as "required" by any regulatory agency.

Members of the Analysis and Display White Paper Project Team reviewed regulatory guidance and shared ideas and lessons learned from their experience. Draft white papers were developed and posted in the PHUSE wiki environment for public comments. Most contributors and reviewers of this white paper are industry statisticians, with input from non-industry statisticians (e.g., Food and Drug Administration [FDA] and academia), and industry and non-industry clinicians. To leverage broad expertise, additional input (e.g., from other regulatory agencies, International Conference on Harmonisation [ICH], World Health Organization [WHO]) for a future version of this white paper would be beneficial to ensure the recommendations meet expectations across the various customers of the data.

2. Scope

This white paper is intended to provide advice to sponsors who are developing the analysis plan for Phase 2-4 clinical trials and integrated summary documents (or other documents that include demographic, disposition, and medication information). Although the focus of this white paper pertains to Phase 2-4, some of the content may apply to Phase 1 or other types of medical research (e.g., observational studies).

Detailed variable specifications for TFLs or dataset development are out of scope. The PHUSE Repository Content and Delivery Project Team will be developing code (utilizing Study Data Tabulation Model [SDTM] and Analysis Data Model [ADaM] data structures from the Clinical Data Interchange Standards Consortium [CDISC]) that are consistent with the concepts outlined in this white paper and placed in the publicly available PHUSE Standard Scripts Repository. The ADaM Implementation Guide (ADaMIG) is considered a key guidance for dataset creation.

3. Definitions

Acronyms

Term	Definition
ADaM	Analysis Data Model
ADaMIG	ADaM Implementation Guide
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDASH	Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CS	Computational Science
DCSREAS	Reason for Discontinuation from Study
DCTREAS	Reason for Discontinuation from Treatment
DS	Disposition domain in SDTM
EU	European Union
FDA	Food and Drug Administration
FR	Federal Register
ICH	International Conference on Harmonisation
ID	Identification
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
OCCDS	Occurrence Data Structure
PHUSE	Pharmaceuticals User Software Exchange
PSAP	Program Safety Analysis Plan
PT	Preferred Term
SAP	Statistical analysis plan
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
TFL	Tables, Figures, and Listings
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

Definitions

Interactive display: A table, figure, or listing created with features that allows the user to change elements of the display, link between displays, and/or see additional data within a display (e.g., with a scroll bar). Examples relevant to clinical trial data include 1) the ability to click a patient identification (ID) to see the patients' individual data, 2) the ability to click a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and a list of patient IDs reporting that preferred term shows up, 3) the ability to click a laboratory analyte, and a plot of values

over time for all patients shows up, 4) the ability to choose a MedDRA level in which to see a summary table for events, 5) the ability to choose which units are preferred for a boxplot over time, 6) the ability to choose an Anatomical Therapeutic Chemical (ATC) level in which to see a summary table for medications, and 7) the ability to choose an ingredient of interest, and all reported medications with that ingredient shows up.

Static display: A table, figure, or listing that is created without any interactive features. It is something that can be viewed in its entirety on a page(s). This is in contrast to an interactive display that allows point-and-click technology and/or scroll bars to see additional data online.

Program safety analysis plan (PSAP): A compound-level planning document describing the planned analyses and definitions required to conduct the planned analyses for Phase 2-3 studies and the Summary of Clinical Safety for a compound [2]. The PSAP may also contain compound-level data collection requirements.

4. Problem Statement

Industry standards for data collection and storage have evolved over time: Clinical Data Acquisition Standards Harmonization (CDASH), observed data (SDTM), and analysis datasets (ADaM). There is now recognition that the next step would be to develop standard TFLs for common measurements across clinical trials and across therapeutic areas. Some could argue that perhaps the industry should have started with creating standard TFLs prior to creating standards for collection and data storage, consistent with end-in-mind philosophy; however, having industry standards for data collection and analysis datasets provides a good basis for creating standard TFLs.

Several regulatory guidance documents contain suggested TFLs and/or discussion around displays and analyses for common assessments, but they are open to varied interpretation. While individual companies may have their own standard TFLs for common data elements, lack of cross-industry standards requires medical reviewers to understand and learn the various nuances and methods across the submissions he/she reviews. In addition, if definitions are different or if the data are displayed in a manner that a medical reviewer is not accustomed to, the sponsor may be asked to summarize the data differently potentially leading to not meeting a first cycle review. Having too many variations in definitions and displays can lead to an unnecessary burden on reviewers. Cross-industry standardization also provides a mechanism to incorporate shared learning more efficiently and potentially enables quicker implementation of new methodologies. Crowd-sourcing standardization efforts (instead of each sponsor networking to maintain their own standards) should lead to more optimal displays for medical reviewers, health authorities, ethics committees, and drug development teams. However, individual companies with mature standardization in place may be hesitant to change to the recommendations in this white paper. The idea is that, over time, the overall review of data will be improved by implementing the latest recommendations and by gaining familiarity of definitions, methods, and displays among all those involved. Using the recommendations in this white paper should lead to more effective and clear communication for all stakeholders.

5. Background

The PHUSE Computational Science Collaboration is an initiative between PHUSE, the FDA, and industry that identified computational science priorities that could be addressed by collaboration, crowd sourcing, and innovation [3]. Several computational science (CS) working groups were created to address many of these challenges. The working group titled “Standard Analyses and Code Sharing” (formerly “Development of Standard Scripts for Analysis and Programming”) has led the development of this white paper, along with the development of a platform for creating and storing shared code.

Several existing guidance documents (see list below) contain suggested TFLs for common measurements. However, these documents generally lack sufficient details to be used as support for the entire standardization effort. Nevertheless, these documents were used as a starting point in the development of this white paper. The documents include the following:

1. Guidance for Industry and Food and Drug Administration Staff: Collection of Race and Ethnicity Data in Clinical Trials (2016) [4]
2. CDISC ADaM Occurrence Data Structure (OCCDS) Version 1.0 (2016) [5]
3. CDISC ADaM Implementation Guide Version 1.1 (2016) [6]
4. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/21/EC (2014) [7]
5. European (EU) Guidance document for the content of the <Co-> critical assessment report (2014) [8]
6. FDA Guidance for Industry: E3 Structure and Content of Clinical Study Reports Questions and Answers (R1) (2013) [9]
7. Japan Format for Preparing the Common Technical Document for Submission of New Drug Applications to Reduce Total Review Time (2011) [10]
8. FDA Manual of Policies and Procedures: Clinical Review Template (2010) [11]
9. European Medicines Agency. A Guideline on Summary of Product Characteristics (SmPC), Revision 2 (2009) [12]
10. FDA Reviewer Guidance. Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (2005) [13]
11. International Conference on Harmonisation (ICH) M4E: Common Technical Document for the Registration of Pharmaceuticals for Human Use - Efficacy (2002) [14]
12. ICH E9: Statistical Principles for Clinical Trials (1998) [15]
13. ICH E3 Guideline for Industry: Structure and Content of Clinical Study Reports (1995) [16]

Additional references used to inform recommendations have been cited throughout the document.

6. Recommendations: General Topics

6.1. General Recommendations

This section discusses general considerations for each type of data collection: demographics, disposition, and prior and concomitant medications or therapy.

6.1.1. P-values

There has been ongoing debate on the value or lack of value of the inclusion of p-values in assessments of demographics, disposition, and medications. This white paper does not attempt to resolve this debate. The controversy usually pertains to safety assessments. Throughout this white paper, p-values have not been included. If a company or compound team decides that these will be helpful as a tool for reviewing the data, they can be included in the display.

6.1.2. Number of Therapy Groups

For this version of the white paper, the example TFLs and suggested methods pertain to two treatment arms (e.g., a low dose and high dose of study drug) versus a comparator (e.g., placebo) for individual studies and one treatment arm versus a comparator for integrated analyses. Most TFLs can be easily adapted to include additional treatment arms or a single arm. The example TFLs indicate a T1&T2 column, which assumes T1 and T2 make sense to group together. If T1 was the study drug and T2 was an active comparator from a different class, then such a column would not be applicable.

6.1.3. Multiple-phase Clinical Trials

The example TFLs for individual studies show two treatment arms versus a comparator within a controlled phase of a study. The example TFLs for integrated summaries show one treatment arm (assumes all of the treated arms are pooled) and a comparator arm within the controlled phase of the studies. Discussion around additional phases such as open-label extensions is considered out-of-scope in this version of the white paper. Many of the TFLs recommended in this white paper can be adapted to display data from additional phases.

6.1.4. Interactive Display

The current predominant practice when creating TFLs for a clinical study report or integrated summary document is to create a set of static TFLs. However, there has been advancement in creating tools that leverage interactive capabilities. An example of such a tool has been contributed to the PHUSE Script Repository and available for public use. Additionally, a PHUSE CS project team (Data Visualizations for Clinical Data) is working on advancing the use of interactive tools. While this white paper focuses on static displays, we do include some notes for areas where interactive capabilities would be beneficial (e.g., having the ability to look at medication data using preferred term, ingredient, or at any ATC level). The current assumption is that if a sponsor or regulatory agency has access to an interactive tool, it can only be used for internal purposes. Thus, for now, the recommendations for an interactive display are limited to TFLs that would not necessarily be expected to be included in a clinical summary report or integrated summary document. Therefore, the recommendations provided in this white paper include primarily static TFLs. Eventually, the hope is that interactive tools can be shared between a sponsor and regulatory agency, or better yet, shared tools can be created via crowd sourcing. When these efforts advance, fewer and fewer static TFLs will be needed.

6.1.5. Integrated Summaries

For submission documents, TFLs are generally created using data from multiple clinical trials. Determining which clinical trials and which treatment arms to combine for a particular set of TFLs can be complex. Although it is not the focus of this white paper to recommend the strategy for integrating studies, typically teams will need to consider both clinical diversity and methodological diversity in order to make decisions regarding which studies should be combined for meta-analysis. Clinical diversity refers to differences in the studies in terms of the subjects, interventions, and outcomes. Methodological diversity refers to differences in how the studies were executed, including study design (e.g., parallel versus crossover blinding) and length of study. In many cases, teams will want to combine more than one subset of studies for meta-analysis. For example, one subset might be all placebo-controlled studies, while another might be all active-comparator studies.

Section 7.4.1 of the FDA Reviewer Guidance [13] contains a discussion of points to consider. For purposes of this white paper, we assume not all studies will have the same doses and that all doses of the investigational study drug that fall within the range of draft label dosing will be included as a single treatment arm. However, the TFLs can be adapted to different scenarios. As discussed in Section 10.1 of the PHUSE Adverse Event White Paper [17], if the treatment-placebo randomization ratio (after pooling of any dose groups) is not constant across the studies included in the integrated summary and only crude percentages are calculated, then the review of data is subject to potential misinterpretations. Similar potential misinterpretations can occur with means (e.g., mean ages). See the PHUSE Adverse Event White Paper [17] for further understanding of paradoxes that can occur when combining data from multiple clinical trials.

6.2. Demographic Measurements

This section will focus on topics associated with demographics measurements.

6.2.1. Variables to Display

One topic that tends to be discussed when creating a demographics table is what variables and categories to display. As mentioned in the Reviewer Guidance [13], the display should include, at a minimum, age, age categories, sex, race, and weight or body mass index (BMI). Other variable (e.g., BMI category) can also be considered for addition to the demographic report. When applicable, the age groups generally include cut-offs at age 65, 75, and 85. When a study is conducted across different countries, counts of subjects by country are generally included. In addition, when a study is conducted across several regions, counts of subjects by regions instead of country are generally included. For studies that include EU member states, per regulation, the population of subjects included in the clinical trial must be listed by each Member State concerned, in the Union as a whole, and in third countries (rest of world). Relevant disease or baseline characteristics can also be combined with

demographics as a single table, but it is often more convenient for reporting purposes to display them on a separate table.

6.2.2. Standard for Defining Race and Ethnicity

The minimum standards for defining race and ethnicity are set by the FDA Office of Management and Budget. At the time of this writing, they were last revised in 1997 [18]. In 2016, the FDA provided clarifying recommendations on maintaining, collecting, and presenting data on race and ethnicity [4]. Currently, there are five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, and White) and two ethnic categories (Hispanic or Latino, and Not Hispanic or Latino). Race and ethnicity are distinct concepts, meaning that a given individual may identify with an ethnic category and to one or more racial categories. Individuals may identify with more than one racial category and should be presented with the option to select all that apply. If race categories are going to be recorded in addition to the five above, then there are cultural sensitivities to take into account to ensure the language is not offensive. Sub-races that can be considered slang or discriminatory should be avoided. Consideration should also be given to applicable laws and regulations of countries when collecting and reporting demographic data. For example, when French subjects are a part of the study, it is not permitted to collect their race; hence, the race of a French subject will always be blank unless special wording was included in informed consents.

6.3. Disposition Information

This section will focus on topics associated with disposition measurements.

6.3.1. Grouping of Reasons for Discontinuation

One topic that tends to be discussed when creating a disposition table is if or how to group the various reasons for discontinuation. Disposition and reason for study discontinuation are important factors in interpreting results of a trial (e.g., studies with a high dropout rate will have additional scrutiny to understand if reasons for discontinuation are associated with a particular treatment and whether the impact of the study medication in a clinical trial setting would also have an impact on patients after it is approved). The CDISC extensible terminology list offers many options as possible reasons to include in collection. When detailed options are included in collection, it is usually desirable to group reasons that are similar, making data interpretation more clearly. A grouped "adverse event" summary provides an overall general assessment of the safety of a compound, especially if treatment differences are detected. Similarly, a grouped "lack of efficacy" (lack of efficacy per subject, lack of efficacy per investigator, etc.) summary provides an overall general assessment of lack of efficacy. For integrated summaries, care is needed when interpreting the data as discussed in Section 6.1.5.

6.3.2. Non-Specific Reasons

Prevention of missing data has gained a fair amount of attention recently [19, 20]. Discontinuation of treatment without a clear reason is considered "missing" information. When a vague reason is cited as a reason for discontinuation (e.g., physician decision, withdrawal by subject, withdrawal by parent/guardian, or other), follow-up is generally required to determine if a more specific reason (e.g., adverse event, lack of efficacy) would be more appropriate. Even when such follow-up occurs, there are often a number of subjects with vague reasons that exist in the data. Additional information (e.g., via a "specify" field) can be reviewed to provide assurance that the reason is unrelated to safety or efficacy. As described in Section 8, a listing is recommended for this purpose. A specify field (or some alternative) would be required during collection to be able to create the listing.

A substantial number of subjects discontinuing due to lost to follow-up is also a sign of concern (as noted in the FDA Safety Reviewer Guidance [13]). Even when aggressive follow-up is implemented to contact subjects, there are often a few subjects who are lost to follow-up. Documenting the attempts to contact a subject will likely be required. However, a specific table or listing in a study report is generally not needed for this purpose.

If the number of subjects who have vague reasons for discontinuation is large for a study, and if the listing of the specify field does not provide assurance that the reasons are unrelated to safety or efficacy (e.g., indicates reasons such as moving away), then additional disposition tables may be required in which the vague reasons are assumed to be safety and/or efficacy-related as a sensitivity analysis. Similarly, if the number of subjects who are lost to follow-up is large, additional disposition tables may be required in which lost to follow-up is assumed to be safety and/or efficacy-related.

6.3.3. Multiple Reasons

Another topic that has been historically discussed when designing disposition collection and/or creating a disposition table is if or how to handle multiple reasons for discontinuation. The Clinical Data Interchange Standards Consortium requires the identification of a primary reason. The guidance for collecting multiple reasons in CDISC is that only the primary reason will appear in the disposition domain in SDTM (DS) and will have an equivalent terminology term in Standardized Disposition Term in SDTM DS domain. Other reasons, if collected, are kept in the supplemental domain. Collection of other reasons appears to be uncommon. Thus, the recommended TFLs in this white paper assume only a primary reason is available for display. However, if multiple reasons are collected, it is important to report all discontinuation information for purposes of being transparent about safety and lack of efficacy.

6.3.4. Study versus Treatment Disposition

One of the initiatives related to prevention of missing data is to encourage subjects to remain in the study and follow the normal schedule of events even when study medication has been discontinued [19, 20]. When such a design is implemented, extra clarity and consideration is required for disposition tables. Prior to such designs, discontinuation from study drug and study was generally synonymous. The details around TFL recommendations for these designs are out-of-scope for this version of the white paper. However, consideration can be given to create both a treatment disposition table and a study disposition table, or include both in a single disposition table. Collection would need to be done at both time points (when the subject discontinues medication and when the subject

discontinues the study) to be able to produce both tables. Fortunately, CDISC now includes information on how this is differentiated in SDTM and ADaM (DCTREAS and DCSREAS).

6.4. Medications

This section will focus on topics associated with medications.

6.4.1. Collection of Medications

When interpreting displays of medications, it is important to understand how medications were collected and the associated instructions. For example, it is important to know whether all medications taken during the study were collected versus a subset (e.g., only medications identified a priori as having a potential impact on the study outcomes). As discussed in the FDA Safety Reviewer Guidance [13], concomitant medications may be assessed as possible predictors of the occurrence of an adverse reaction. Also, they are often very helpful for individual case assessment (See Table 7.1.7.5.1 hepatotoxicity example from the FDA Safety Reviewer Guidance [13]). For compounds early in development, it is generally unknown which medications could end up being relevant for these purposes. Therefore, collecting all medications is generally recommended.

6.4.2. Classifications of Medications

When summarizing medications used in a study, it is very useful to utilize a classification system such that the same drugs are grouped together regardless of how the drug was listed in collection (e.g., generic name versus trade name). The WHODrug dictionary is one such system and is commonly used in global studies [21]. In a March 2015 Federal Register (FR) Notice [22], the FDA indicated their preference to provide WHODrug dictionary codes for concomitant medication data in investigational studies provided in regulatory submissions. They indicated that the codes include the drug product trade name where available, the active ingredient(s), and ATC class. This desired format was later reflected in the March 2016 version of the Technical Conformance Guide [23]. At the time of this writing, the current version of the Technical Conformance Guide [24], published in October 2017, continues to reflect this expectation.

At the time of the March 2015 FR Notice [22], WHODrug dictionary [21] preferred names (B2/C formats) included a mix of trade names and ingredients making it difficult for medical reviewers. The format of the WHODrug Global dictionary was updated in March 2017 (B3/C3 formats) and dictionary types were consolidated as WHODrug Global in September 2017 to facilitate CDISC SDTM compliance and improve the usability of the concomitant medication information collected in clinical trials for both users and regulators [25]. A majority of the multi-ingredient records in the B2/C formats have the first entered trade name of their respective ingredient combinations as the preferred name. For single ingredient records, the active substance (i.e., generic name,) is the preferred name. In the B3/C3 formats, the preferred names are generic for both single and multi-ingredient records (i.e., they represent the substance or substance combination). Within the WHODrug Global B3/C3 format, the field length of the drug name has been extended substantially.

The FDA published updates to three documents in October 2017 providing additional information regarding their recommendation/requirement to use the WHODrug Global dictionary for coding of concomitant medications in clinical trial electronic submissions of new drug applications, abbreviated new drug applications, biologics license applications, and certain investigational new drug applications:

- Federal Register [26]
- FDA Data Standards Catalog [27]
- Study Data Technical Conformance Guide [24]

The updated FDA guidances specify that the most current WHODrug Global B3 format annual version will be required in submissions for studies that start after March 15, 2019. None of these informs expectation regard the summary table of medication data in clinical study reports or submissions. Of note, while these updated FDA guidances provide expectations around medication coding and data, these guidances do not include advice specific to summary tables for clinical study reports or submissions. The updates clearly improve the usability of concomitant medication information when individual patient data is reviewed. However, exactly how to leverage the improvements in coding and data storage for the purpose of summary tables is less clear and subject to debate as discussed in Section 7.2.2.

The WHO Collaborating Centre for Drug Statistics Methodology maintains the official ATC hierarchical classification system. The ATC classes within the WHODrug Global B3/C3 format dictionaries are maintained by the Uppsala Monitoring Centre (UMC) [21]. The ATC classes in WHODrug Global dictionary may be official (consistent with the WHO classification system) or unofficial (UMC may assign additional ATC hierarchy codes to a preferred name, or create completely new ATC codes). The official ATC categories include five levels of classification and are based on the organ or system on which a drug acts and/or the chemical, pharmacological, and therapeutic properties of the drug. The fifth level of the official ATC hierarchy represents active substances and is not included within WHODrug Global dictionary. Every generic drug is assigned to one or more ATC code. A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses. Decisions need to be made on which ATC code(s) will be stored in the data (in which case, indication for use may become important) versus all possible ATC codes. For special topic medication analyses using ATC levels, all records associated with the active substances within the ATC level would typically be included. It is unlikely that records would be excluded based on primary class selection. Variables that capture intended use information such as medication indication or route may not be collected within a study or available for primary ATC selection. The quality of the data collected in these fields may also be insufficient for primary ATC assessment. Anatomical Therapeutic Chemical categories may be helpful, particularly for medications of special interest. However, for many medications of special interest, use of WHODrug Global Standardized Drug Groupings or custom drug groupings of relevant medications is often required due to limitations of ATC categories.

Of note, unlike MedDRA coding, not all levels of ATC are automatically populated. Thus, if an analysis is planned for a particular level of ATC, the study team will need to ensure that the level is populated for all medications or adjust

analytical planning to handle having different levels for different medications. Furthermore, if an analysis is planned utilizing the primary ATC class across multiple studies, the methodology for determining the primary ATC code needs to be the same in all the studies in the analysis. If the methodology is not the same in all the studies, teams may end up with unhelpful situations where the same medication, taken for the same indication for use is mapped to one ATC code in one study and another in another study. (e.g., "ACETYLSALICYLIC ACID" that was administered for the same indication for use in two patients in two studies could be mapped to the primary ATC code "B01AC" (PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN) in one study and "A01AD" (OTHER AGENTS FOR LOCAL ORAL TREATMENT) in the other study.

6.4.3. Units

A medication unit is the basic measure of the amount of medication taken. Medication dosage amount and units of measurement may or may not be collected for a study. Study teams need to decide the analytical plans for medications to inform the decision whether to collect units for concomitant medications. Some companies convert collected units into a standard set of units. However, some dose formulations, such as medications in the form of ointment or powder, do not have associated units of measurement.

6.4.4. Partial Dates

The start/stop date of a medication represents the beginning and end of the period in which the medication was or is being used. Whenever possible, the complete date(s) of use of a medication should be obtained rather than an estimate such as "2007." For data submitted in CDISC format, the dates displayed will follow the International Organization for Standardization, ISO 8601, which provides a text-based representation of dates and time. If, for example, a date is collected as December 2003 with unknown day, then a date in ISO 8601 format is 2003-12. If the date values are completely missing the field should be blank (null).

6.4.5. Repetition

When a medication is taken repeatedly, multiple records for the same medication with different start dates (times) might cause it to be counted as both a prior medication and a concomitant medication. A decision must be made whether to group all medications of the same name (or mapping to the same terminology using a coding system) under a single start date or to treat them as independent records. In this white paper, we recommend treating them as separate records so that medication can be included in both prior and concomitant medications summary tables. How medication data is handled should be clear to the reader of the report. In general, when multiple records exist for the same prior or concomitant medication, all records should be displayed on listings. However, summary reports should count each medication only once in each study period that the usage occurred.

7. Recommendations: Tables and Figures for Individual Studies

7.1. Recommended Displays

Table 7.1 shows the recommended display for demographics data. As noted in Section 6.2.1, including age, age categories, sex, race, and weight or BMI at a minimum is recommended. This display allows for easy incorporation of both categorical and continuous variables by listing statistics as rows instead of columns. The total column is included, as a summary for the entire population (instead of by treatment) is often desired. Age categories will vary depending on the study population. However, for adult studies, there is an expectation for cut-offs at 65, 75, and 85 when applicable [14]. For studies that include young subjects, further delineation will be necessary (e.g., newborns [0-27 days], infants and toddlers [28 days – 23 months], children [2-11 years], and adolescents [12-17 years]). For continuous variables, displaying the mean, standard deviation, median, 25th and 75th percentile, minimum, and maximum are all recommended for an understanding of a population's distribution. Multi-racial subjects should be combined in an ATC single "multiple race" category for summary purposes. Specific racial combinations are available in the demographics datasets, if needed, for individual subject descriptions. The count of subjects with non-missing values for each variable is used as the denominator, which allows for percentages that are more meaningful. The listed races and ethnicity are consistent with "Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials" [4].

Figure 7.1 is a recommended display in flowchart format that shows the number of subjects, who screened, entered, randomized, took medication, discontinued, and completed. This flowchart may need to be hand generated as opposed to writing a program to create it. Such displays are very useful in providing a high-level summary of subject numbers and are similar to ANNEX IVb in the ICH E3 guidance [16]. The figure is just an example and would need to modify as needed per the design of the study and/or population definitions used for analyses.

Table 7.2 is the recommended display for a more in-depth study disposition summary, and the specific rows would match the choices provided in collection for the study. This table can be repeated for each phase of a multi-phase trial. It is recommended that the table include all reasons that were identified as a reason by at least one subject and a summary percentage for related reasons grouped together. The reasons are consistent with CDISC SDTM controlled terminology. Table 7.3 is essentially the same as Table 7.2 except it is an example of when grouping reasons is not required because the collected reasons are sufficiently broad.

Listing 7.1 is recommended as a means to provide assurance that those who listed physician decision, withdrawal by subject, withdrawal by parent/guardian, or other as the reason for discontinuation were truly unrelated to an adverse event or lack of efficacy. Such a listing requires a textual description (e.g., "specify" field) to be collected when one of the less specific reasons is checked. Because such reasons are specifically reviewed for adverse events or lack of efficacy during data collection and monitoring, sponsors of a clinical trial may be in the position to provide specific documentation of the true reason.

Table 7.4 is a recommended display for medications taken prior to study drug (but still summarized by treatment group). These generally include medications that subjects take during the screening period. Specifically, prior medications can be defined as those medications taken prior to the initial dose of study drug. In many cases, prior medication helps to understand the characterization of the population. The general recommendation is to present this table using WHODrug Global dictionary preferred names, although alternatives (by ATC code, by ingredient) should be acceptable. For internal purposes, an interactive tool can be developed that allows for selecting between preferred name, ATC code, or ingredient for a sponsor's medical review. However, such capabilities might be difficult to achieve in the short term, especially for a display by ingredient, as data by individual ingredient is not usually created.

Table 7.5 is a recommended display for medications taken concomitantly with study drug, regardless of whether the medication was also taken prior to study drug. This table provides an overall summary of medications taken by subjects during the controlled phase of a study and can be reviewed by medical personnel to gain a greater understanding of the population in the study. The general recommendation is to present this table using WHODrug Global dictionary preferred names. As with prior medications, alternatives (by ATC code as shown in Table 15.1, or by ingredient as shown in Table 15.2) should be acceptable, and ideally an interactive tool can be developed that allows for selecting between preferred name, ATC code, or ingredient. As with all data that benefit from being consistent across clinical development program for that compound, the specifics for medication should be documented in the compound's PSAP [2, 28, 29, 30] or similar planning document that is developed early in a compound's lifecycle and shared with regulatory agencies for feedback as needed.

Table 7.6 is a recommended display for medications of interest sorted by the medication grouping of interest (e.g., specific ATC class or Standardized Drug Grouping [SDG]). It includes the individual medication along with the grouped medication (subjects are still counted only once) similar to adverse event preferred terms nested in System Organ Class or Standardized MedDRA Query (SMQ) when using a hierarchical dictionary such as the MedDRA. This table would only be needed if there were at least one medication grouping of interest. Examples include:

- ACEBUTOLOL and ATENOLOL under the grouping "BETA BLOCKING AGENTS, SELECTIVE" (ATC Level 4 Class)
- ADALIMUMAB and CHONDROITIN;COLLAGEN;GLUCOSAMINE under the grouping "Biologic DMARDs" (Standardized Drug Grouping)

Listing 7.2 is a listing of all medications taken during the study. This listing allows easy access to additional information (e.g., dose) that may be of interest. This listing would not necessarily need to be included in clinical study reports. If a sponsor has access to an interactive tool that allows their internal medical personnel easy access to this data, a static listing may not be needed.

Table 7.1.

Demographic Summary <Insert population (for example, Safety Population (N = xxx))>
<Insert study ID(s) or description of database utilized Study Phase or phases (if needed)

Demographic Parameter		PL (N=XXX)	T1 (N=XXX)	T2 (N=XXX)	T1 & T2 (N=XXX)	Total (N=XXX)
Sex n (%)	n[a]	xx	xx	xx	xx	xx
	Female	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Male	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Missing	xx	xx	xx	xx	xx
Age (years)	n[a]	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Q1, Q3	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	Missing	xx	xx	xx	xx	xx
Age Categories n (%)	n[a]	xx	xx	xx	xx	xx
	<65	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	>65 and <75	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	>75 and <85	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	>85	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Missing	xx	xx	xx	xx	xx
	>65	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	>75	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Race n (%)	n[a]	xx	xx	xx	xx	xx
	American Indian or Alaska	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Native	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Asian	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Black or African American	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Native Hawaiian or Other Pacific Islander	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	White	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Multiple	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Missing	xx	xx	xx	xx	xx
Ethnicity n (%)	n[a]	xx	xx	xx	xx	xx
	Hispanic or Latino	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
	Not Hispanic or Latino	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)	xx (x.x)
Weight (kg)	n[a]	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Q1, Q3	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	Missing	xx	xx	xx	xx	xx
Country n (%)	n[a]	xx	xx	xx	xx	xx
	Country 1	xx.x	xx.x	xx.x	xx.x	xx.x
	Country 2	xx.x	xx.x	xx.x	xx.x	xx.x
	Country n	xx.x	xx.x	xx.x	xx.x	xx.x
	Missing	xx	xx	xx	xx	xx

Abbreviations: N = number of subjects in the population; PL= Placebo; Q1=25th Percentile; Q3= 75th Percentile; SD=Standard Deviation; T=Treatment.

[a] Number of subjects with non-missing data, used as the denominator.

Figure 7.1. Subject Dispositions

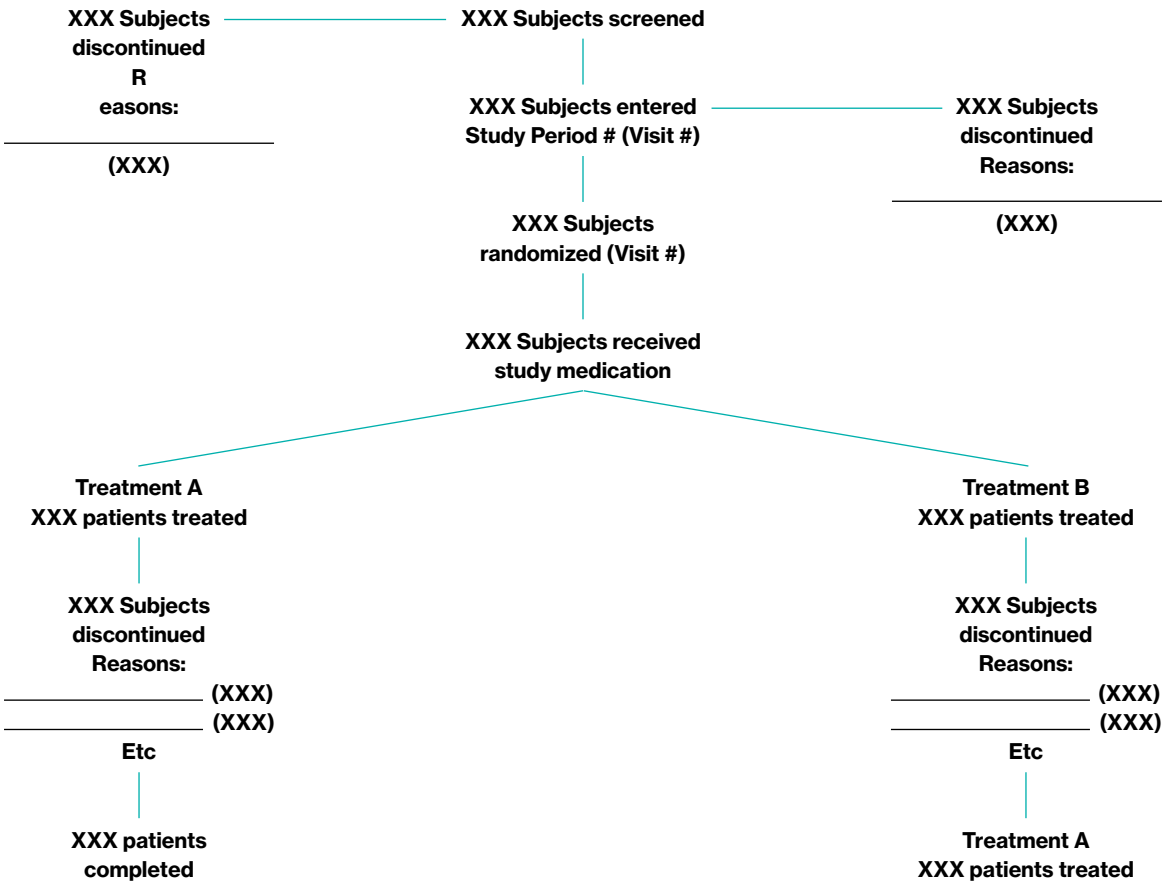

Table 7.2.

Summary of Study Disposition [Option A]
<Insert population (for example, Safety Population (N = xxx))>
<Insert study ID(s) or description of database utilized Study Phase or phases (if needed)

Study Disposition	PL (N=XXX) n (%)	T1 (N=XXX) n (%)	T2 (N=XXX) n (%)	T1 & T2 (N=XXX) n (%)	Total (N=XXX) n (%)
Completed the study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death or Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons related to lack of efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Progressive Disease	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Disease Relapse	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other Reasons	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-Compliance with Study Drug	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician Decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = total number of subjects in the population; n = number of subjects in the specified category; P=Placebo; T=Treatment.

Note: The specific rows should match the choices provided in collection for the study; %=Percentage of subjects with N as the denominator.

Table 7.3.

Summary of Study Disposition [Option B]
<Insert population (for example, Safety Population (N = xxx))>
<Insert study ID(s) or description of database utilized Study Phase or phases (if needed)

Study Disposition	PL (N=XXX) n (%)	T1 (N=XXX) n (%)	T2 (N=XXX) n (%)	T1 & T2 (N=XXX) n (%)	Total (N=XXX) n (%)
Completed the study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-Compliance with Study Drug	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician Decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = total number of subjects in the population; n = number of subjects the specified category; P=Placebo; T=Treatment.

Note: The specific rows should match the choices provided in collection for the study; %=Percentage of subjects with N as the denominator.

Listing 7.1.

<Enrolled / Randomized> Population – Subjects who discontinue study due to physician decision, withdrawal by subject, withdrawal by parent/guardian, or other
Study phase <Insert study ID(s) or description of database utilized Treatment: T1

Subject ID	Reason for Discontinuation	Specific Detail Reason
101001	aaaa	xxxxxx
101004	aaaa	xxxxxx
ETC		

Table 7.4.

Summary of Prior Medications by Preferred Name in Descending Frequency of T1 & T2
<Insert population (for example, Safety Population (N = xxx))>
<Insert study ID(s) or description of database utilized Study Phase or phases (if needed)

Prior Medications
Title (optional; add more if needed)
<Insert population (for example, Safety Population (N = xxx))>
<Insert study ID(s) or description of database utilized Study Phase or phases (if needed)

Study Disposition	PL (N=XX) n (%)	T1 (N=XX) n (%)	T2 (N=XX) n (%)	T1 & T2 (N=XX) n (%)	Total (N=XX) n (%)
Completed the study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-Compliance with Study Drug	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician Decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N=number of subjects; n=number of subjects taking the medication.

Note: Prior Medications include medications that subjects take during the screening period; %=Percentage of subjects with N as the denominator. Subjects may be counted in more than one row.

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Table 7.5.

Summary of Prior Medications by Preferred Name in Descending Frequency of T1 & T2
<Insert population (for example, Safety Population (N = xxx))>
<Insert study ID(s) or description of database utilized Study Phase or phases (if needed)

Preferred Name	PL (N=XX) n (%)	T1 (N=XX) n (%)	T2 (N=XX) n (%)	T1 & T2 (N=XX) n (%)	Total (N=XX) n (%)
Subjects with >=1 concomitant medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #3]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N=number of subjects; n=number of subjects taking the medication.

Note: Subjects may be counted in more than one row; %=Percentage of subjects with N as the denominator.

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Table 7.6.

Summary of Concomitant Medication within Classes of Interest <Insert population (for example, Safety Population (N = xxx))> <Insert study ID(s) or description of database utilized Study Phase or phases (if needed)

Preferred Name	PL (N=XX) n (%)	T1 (N=XX) n (%)	T2 (N=XX) n (%)	T1 & T2 (N=XX) n (%)	Total (N=XX) n (%)
Subjects with >=1 concomitant medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Medication Class Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #3]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Medication Class Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Name #3]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N=number of subjects; n=number of subjects taking the medication.

Note: Subjects may be counted in more than one row; %=Percentage of subjects with N as the denominator.

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Listing 7.2.

Listing of Medications
<Insert population (for example, Safety Population (N = xxx))>
<Insert study ID(s) or description of database utilized Study Phase or phases (if needed)
Treatment: Treatment A

Subject ID	Medication	ATC term(s)	Preferred Name	Dose (Unit)	Primary indication For use	Start date/ Stop date	Dur. (days)	Cont. (Y/N)
101001	YYYY	AnIIIIII ii AmIIIII	Valsartan	xxx	Concomitant	2012-12-15/	BB	N
	XXXX	ANTTTTTT		xxx	Illness	2013-YYY-15		
101004	YYYY	ZZIIII	inhibitors Enalapril	xxx	Concomitant	2012-12/		Y
ETC								

Abbreviations: Dur=Duration; N=No; Y=Yes; Cont=Continue.

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7.2. Discussion

7.2.1. During the development of Version 1

For a summary of the discussion during the development of Version 1 of this white paper, see Section 7.2 in the first version, which can be found in the PHUSE Computational Science Deliverables Archive [31]. In summary, the recommended demographic and disposition tables were developed with little controversy. For medications, there was consideration given to not recommending any summary and listing table for prior and concomitant medications, as there are no regulatory requirements for summary tables, and having the data available for individual case assessment could be sufficient. In the end, summary tables were recommended. Consideration was also given to whether to recommend a summary table that utilizes the different ATC categorizations. It was determined that such complex summaries were not generally warranted and perhaps most useful in the ad-hoc context. However, summarizing by ATC code is certainly an option for the general summary table.

7.2.2. During the development of Version 2

During the development of version 2, discussion primarily pertained to the potential impact of moving to WHODrug Global B3/C3 formats for medications. As discussed in Section 6.4.2, with the B3/C3 formats, the preferred names are generic for both single and multi-ingredient records. So, for multi-ingredient medications, while the preferred name becomes more medically useful, the names can become very long (e.g., arginine;ascorbic acid;betacarotene;biotin;calcium carbonate;calcium phosphate;chromium;colecalciferol;copper; cyanocobalamin;dl-methionine;folic acid;glutamic acid;inositol;iodine;iron;lecithin;lysine; magnesium oxide;manganese;nicotinic acid;pantothenic acid;papain;pyridoxine;riboflavin; selenium;thiamine;tocopherol;tyrosine;yeast;zinc). Very long names will make the summary table cosmetically undesirable. This led to a discussion of the purpose for summarizing medication data and the advantages and disadvantages of the various options for summarizing medication data. As noted in Section 6.4.2, while the updated FDA guidance outlines improvements for coding and data, it does not include advice for summary tables. The project team did not infer that the desire for better coding in data necessarily meant that summary tables must be created using ingredients and/or ATC codes.

For the summary table of concomitant medications for a controlled treatment period, we believe the primary purposes are 1) for medical (from sponsors and regulatory agencies) to have an idea of the types of medications subjects are taking so, when safety data are reviewed, medical will know whether a particular finding could be influenced by frequent use of a particular concomitant medication, and 2) to determine if there are any medications that are used at substantially different rates between treatment and control that would be important to understand when reviewing the safety or efficacy data. Table 7.7 provides a summary of the identified advantages and disadvantages for four options that were discussed within the project team.

Table 7.7.

Summary of Concomitant Medication Display Options

Display Option	Advantages	Disadvantages
By Preferred Name (Table 7.5)	• Easy to implement. • Easy to understand. • Each medication is represented once in the table, which is intuitively desirable.	• Medical team may need to look across multiple rows to determine if there is an imbalance between treatment and control for an ingredient. If an ingredient is taken as part of multi-ingredient drug, it will be included across the various combinations. • It may be difficult to identify a class effect or imbalance (e.g., beta-blockers listed throughout table based on individual substance frequency, rather than pharmacologic class). • Long preferred names will make the table cosmetically undesirable.
By Preferred Name within ATC code (medications assigned to a single ATC code) (Table 15.1)	• Grouping medications into higher-level categories can be useful.	• Given the purpose, having medications sorted for their reason for taking the medication may not be relevant. • The same generic substance may be listed more than once under different ATC class codes, depending on reported intended use. • Medical may need to look across multiple rows to determine if there is an imbalance between treatment and control for an ingredient. • Long preferred names will make the table cosmetically undesirable. • Study teams will need to ensure that the level that is used for analysis is actually populated for all medications, or adjust analytical planning to handle having different levels for different medications. • For displays across multiple studies, the method for assigning a primary ATC code would need to be consistent. • Intended use variables may not be collected or be of sufficient quality to support primary ATC Class selection. • Primary ATC Class selection is resource intensive and exponentially increases volume of data requiring coding (classification based on combination of multiple variables rather than single variable). • Variable combinations have to be re-assessed when up-versioning the data.
By Preferred Name within ATC code (medications assigned to all applicable ATC codes) (Table 15.1)	• Grouping medications into higher-level categories can be useful.	• Medications will appear in more than one location, which can be confusing. • Some ATCs can appear that do not accurately represent the data (e.g., "drugs taken for eye disorders" might appear when no one took a medication for an eye disorder), which can be confusing. • Long preferred names will make the table cosmetically undesirable.
By Ingredient (Table 15.2): Patients taking multi-ingredient drugs would be counted toward each ingredient.	• Likely the most relevant for the assumed purposes. • Cosmetically the most desirable.	• The information on whether the ingredient was taken as a single-ingredient drug versus part of a multi-ingredient drug would be lost. • An extra step is needed to implement – A separate ADaM dataset would need to be created to facilitate the separation of multi-ingredient drugs, or separating multi-ingredient drugs would need to be handled in the programming for the summary table. • Some users of the table might find it difficult to understand how multi-ingredient drugs are represented (that one medication is represented under each ingredient).

In the end, summarizing by preferred names is what was decided for the general recommendation, as it is the most practical and is likely the display that requires the least amount of explanation. However, the other displays should be considered acceptable to regulatory agencies (as there is not even a regulatory requirement for any summary table). We do not believe multiple displays should be expected in clinical study reports. The recommendation may change in future versions of this white paper as we learn more about how users of this table prefer to see the data.

8. Recommendations: Tables and Figures for Integrated Summaries

In general, many of the TFLs recommended in Section 7.1 of this white paper can be adapted for the integrated summaries [32, 33]. If the team does decide to include p-values, the Cochran-Mantel-Haenszel general association test (or row mean scores as appropriate) stratified by study is recommended for categorical variables and analysis of variance with study as a blocking factor is recommended for continuous variables. Study-size adjusted percentages (references) are also recommended when warranted. See the PHUSE Adverse Event White Paper [17] for a discussion.

9. Recommendations: Example Statistical Analysis Plan Language

The following is example language that study teams can start with when developing a Statistical Analysis Plan:

The planned summaries of demographic, disposition, and concomitant medication are based on the recommendations provided in a white paper produced by PHUSE Computational Science Working Group collaboration with the FDA and PHUSE). The white paper includes justifications for the choices. Specifically, the following white paper pertains: Analyses and Displays Associated with Demographics, Disposition, and Medications in Phase 2-4 Clinical Trials and Integrated Summary Documents (*http://www.phuse.eu/CSS-deliverables.aspx*).

Not all displays described in this plan will necessarily be included in the clinical study report. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display described in this plan and not provided would be available upon request.

A summary table will be generated for subject demographics. Variables to be included are sex, age, age categories, race, ethnicity, weight, and country. Age categories include <65, ≥65 to <75, ≥75 to <85, ≥85, ≥65 and ≥75. For continuous variables, the following statistics will be provided: the number of subjects, mean, standard deviation, minimum, maximum, median, 25th and 75th percentile. For categorical variables, percentages will be calculated using the number of subjects with non-missing data for the specific variable.

Reasons for study discontinuation by treatment group will be summarized. In addition to each reason, a summary of the adverse event-related reasons (death or adverse event) and a summary of the efficacy-related reasons (lack of efficacy, progressive disease, and disease relapse) will be provided. Subject disposition will be displayed in a flowchart showing number of subjects screened, entered, randomized, received medication by treatment, discontinued across all study periods by treatment, and completed by treatment.

The proportions of subjects who received previous therapy will be summarized by WHODrug Global dictionary preferred names. The proportions of subjects who receive concomitant medications during the acute treatment phase, regardless of whether the medication was also taken prior to study drug, will be summarized by WHODrug Global dictionary preferred names.

10. Disclaimer

The opinions expressed in this document are those of the authors and should not be construed to represent the opinions of PHUSE members' respective companies or organizations or FDA's views or policies. The content in this document should not be interpreted as a data standard and/or information required by regulatory authorities.

11. Revision History

Date	Author	Version	Changes
07 October 2014	See Section 12	v1.0	First edition
02 March 2018	See Section 12	v2.0	• Shells were updated to include two treatments arms and placebo instead of just one treatment arm and placebo. • Additional discussion was added on concomitant medications given updates in WHODrug Global B3 format. • Discussion was added where interactive tools could be leveraged. • Additional relevant guidance documents and new references were added. • "Subjects" is used instead of "patient" to be consistent with CDISC controlled terminology.

12. Acknowledgements

Version 1:

The key contributors include Simin K. Baygani and Mary E. Nilsson.

Additional contributors include: Cathy Bezek, Adrienne Bonwick, Nancy Brucken, Arthur Collins, Sue DeHaven, Dany Guerendo, Kathy Li, Mercidita Navarro, Pierre Nicolas, Regina G. Nye, John R. Schoenfelder, Dirk Spruck, Christos Stylianou, Terry Walsh, and Wei Wang.

Version 2:

The key contributors include Simin K. Baygani.

Additional contributors/reviewers (e.g., participated in discussions, provided review comments on portions of the content) include: Nancy Bauer, Nhi Beasley, Cathy Bezek, Nancy Brucken, Brenda Crowe, Susan Duke, Lei Gao, Lisa Houterloot, Karin LaPann, Kim Musgrave, Mereidita T. Navarro, Russ Newhouse, Mary Nilsson, Casie Polanco, Marlo Searcy, Julie Shah, Jun Takeda, Lothar Tremmel, Lori VanMeter, Terry Walsh, Wei Wang, Aiming Yang, and Xiaoping Zhang.

Apologies to contributors/reviewers that we may have missed.

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15. Appendix A: Tables and Figures Considered, but Not Part of Recommendations

Table 15.1.

Summary of Concomitant Medications by Anatomic Therapeutic Chemical (ATC) Level
Title (optional; add more if needed)
<Insert population (for example, Safety Population (N = xxx))>
<Insert study ID(s) or description of database utilized
Study Phase or phases (if needed)

Abbreviations: N=number of subjects; n=number of subjects taking the medication.

Note: Subjects may be counted in more than one row; %=Percentage of subjects with N as the denominator.

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ATC Level	PL (N=XX) n (%)	T1 (N=XX) n (%)	T2 (N=XX) n (%)	T1 & T2 (N=XX) n (%)	Total (N=XX) n (%)
ATC Level 1 term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 2 term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 3 term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<more terms>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 term n	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 3 term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<more terms>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Level 4 term n	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 15.2.

Summary of Concomitant Medications by Ingredient in Descending Frequency of T1 & T2
Safety Population

Preferred Term	PL (N=XX) n (%)	T1 (N=XX) n (%)	T2 (N=XX) n (%)	T1 & T2 (N=XX) n (%)	Total (N=XX) n (%)
Subjects with >=1 concomitant medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Ingredient #1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Ingredient #2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Ingredient #3]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N=number of subjects; n=number of subjects taking the medication.

Note: Subjects may be counted in more than one row; %=Percentage of subjects with N as the denominator.

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