1. Analyses and Displays Associated with Demographics, Disposition, and Medications in Phase 2-4 Clinical Trials and Integrated Summary Documents

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A White Paper by the PhUSE Computational Science Development of Standard Scripts for Analysis and Programming Working Group

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3. Revision History

Version 1.0 was finalized 07 October 2014.

4. Purpose

The purpose of this white paper is to provide advice on displaying, summarizing, and/or analyzing demographics, disposition, and medication (prior and concomitant therapy) data in 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 industry standards with respect to analysis and reporting for measurements that are common across clinical trials and across therapeutic areas. In particular, this white paper provides recommended tables, figures, and listings for demographics, disposition, and medications. Different white papers have been completed or are in progress providing recommended tables, figures, and listings for other data that are common (e.g., laboratory measurements, vital signs, electrocardiograms, adverse events).

This advice can be used when developing the analysis plan for individual clinical trials, integrated summary documents, or other documents which 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).

Development of standard Tables, Figures, and Listings (TFLs) and associated analyses will lead to improved standardization from collection through data storage. How the results will be analyzed and reported must be known before finalizing how to collect and store the data. The development of standard TFLs will also lead to improved product lifecycle management by ensuring reviewers receive the desired analyses for the consistent and efficient evaluation of patient safety and drug effectiveness. Although having standard TFLs is an ultimate goal, this white paper reflects recommendations only and should not be interpreted as “required” or even suggested by any regulatory agency.

Detailed specifications for TFL or dataset development are considered out-of-scope for this white paper. However, the hope is that specifications and code (utilizing SDTM and ADaM data structures) will be developed consistent with the concepts outlined in this white paper, and placed in the publicly available Standard Scripts Repository.

5. Introduction

Industry standards have evolved over time for data collection (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.

The beginning of the effort leading to this white paper came from the PhUSE Computational Science Collaboration, an initiative between PhUSE, FDA, and Industry where key priorities were identified to tackle various challenges using collaboration, crowd sourcing, and innovation (Rosario, et. al. 2012). Several Computational Science (CS) working groups were created to address a number of these challenges. The working group titled "Development of Standard Scripts for Analysis and Programming" has led the development of this white paper and other white papers covering common domains as well as the development of a platform for storing shared code. Contributors to this white papers are industry statisticians, statistical programmers and clinicians; with various input from other non-industry entities such as the FDA and academia statisticians. We hope for more collaboration from others for future versions of this white paper.

Several existing documents contain suggested TFLs for common measurements. However, many of these documents are now relatively outdated, and 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:

- ICH E3: Structure and Content of Clinical Study Reports
- ICH E9: Statistical principles for clinical trials
- Guideline for Industry: Structure and Content of Clinical Study Reports
- Reviewer Guidance. Conducting a Clinical Safety Review of a New Product Application and. Preparing a Report on the Review
- ICH M4E: Common Technical Document for the Registration of Pharmaceuticals for Human Use - Efficacy
- Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials
- 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 2001/20/EC

This white paper provides recommendations for TFLs and does not specifically address SDTM and ADaM requirements. The ADaM Implementation Guide (ADaMIG) is considered a key guidance for dataset creation.

6. General Considerations

6.1. All Measurement Types

This section discusses general considerations for each type of data collection: demographics, disposition, 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. Using p-values for the purpose of describing a population is generally considered to have no added value. 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 one treatment arm versus a comparator. Displays and methods for multiple treatment arms are out-of-scope for this version of the white paper, but are planned for future versions.

6.1.3. Multi-phase Clinical Trials

The example TFLs show one treatment arm versus comparator within a controlled phase of a study. 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. Integrated Summaries

For submission documents, TFLs are generally created using data from multiple clinical trials. Determining which clinical trials to combine for a particular set of TFLs can be complex. Summaries of demographics and medications are generally created to characterize the population and not to assess treatment comparisons. When comparisons between treatments are made, understanding whether the overall representation accurately reflects the review across individual clinical trial results is important.

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 what categories to display. As mentioned in the Reviewer Guidance, the display should at a minimum include age, age categories, sex, race, and weight. Other optional variables such as body mass index (BMI) and BMI category can also be considered to be added to the

demographic report. When applicable, the age groups generally include cut-offs at age 65 and age 75. When a study is conducted across different countries, counts of subjects by country are generally included. Also, when a study is conducted across several regions, counts of subjects by regions instead of country are generally included. For studies which 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 sometimes 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 (OMB). At the time of this writing, they were last revised in 1997. 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. 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 a bit easier. A grouped “adverse event” summary provides an overall general assessment of the safety of a compound. A grouped “lack of efficacy” (lack of efficacy per subject, lack of efficacy per investigator, etc.) summary provides an overall general assessment of efficacy. Both can be very useful.

6.3.2. Non-Specific Reasons

Prevention of missing data has gained a fair amount of attention recently (National Research Council 2010, O'Neill and Temple 2012). 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 such 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 7, 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). Even when aggressive follow-up is implemented to try to contact subjects, there are often at least some 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 in the final data for a study, and if the listing of the specify field does not provide assurance that the reasons are unrelated to safety or efficacy, then additional disposition tables may be required in which the vague reasons are assumed to be safety and/or efficacy-related. 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. CDISC 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 domain DS and will have an equivalent terminology term in DSDECOD. 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.

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 (National Research Council 2010, O'Neill and Temple 2012). When such a design is implemented, extra clarity and consideration is required for disposition tables. Prior to such designs, discontinuation from medication and study was generally synonymous. Thus, discontinuation from the study due to an adverse event is generally interpreted as discontinuation from medication. 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. 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.

6.4. 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's 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, 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 Reviewer Guidance, Safety Review Guidance). 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. Classification 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 World Health Organization (WHO) Drug Dictionary is one such system and is commonly used in global studies. Utilizing the WHO Drug Dictionary preferred names is one way to summarize medications, and is often sufficient. However, it should be noted that WHO Drug Dictionary preferred names do contain Trade names instead of ingredients for combination drugs.

WHO also maintains Anatomical Therapeutic Chemical (ATC) categories. At one point, such categories were expected in CDISC datasets, but it is no longer the case. ATC categories include 5 levels of classification and are based on the organ or system on which a drug acts and/or the chemical, pharmacological, and therapeutic properties. Every drug is assigned to at least one ATC code. Many drugs can belong to more than one ATC code. 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 based on analytical needs. How coding is done and stored in the data is very important for how the information can be used for analysis and reporting. ATC categories may be helpful (if done correctly) but are generally considered unnecessary when simply providing a summary of the medications used in a study.

Due to the limitations of WHO Drug Dictionary preferred terms and ATC categories, manually grouping medications relevant to special topics is often required. Categorizing medications for topics of special interest is considered out-of-scope for this white paper.

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. Some companies convert collected units into a standard set of units. However, some dose formulations, such as asthma medication in the form of a 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 time 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 to reflect them as both prior and concomitant medications. 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. 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, 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 and 75 (ICH M4E: Common Technical Document for the Registration of Pharmaceuticals for Human Use - Efficacy). For studies that include young patients, further delineation will be necessary [e.g., newborns (0-27 days), infants and toddlers (28 days – 23 months), children (2-11 years), adolescents (12-17 years)]. For continuous variables, displaying the mean, standard deviation, median, Q1, Q3, min, and max are all recommended for an understanding of a population's distribution. Multi-racial subjects should be combined in a single "multiple race" category for summary purposes. Specific racial combinations are available in the demographics datasets, if needed for individual patient descriptions. The count of patients with non-missing values for each variable is used as the denominator, which allows for more meaningful percentage. The listed races and ethnicity are consistent with "Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials".

Figure 7.1 is a recommended display in flowchart format that shows the number of patients who entered, enrolled, 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 patient numbers, and are similar to ANNEX IVb in the ICH E3 guidance. Table 7.2a is the recommended display for a more in-depth disposition summary. This table can be repeated for each phase of a multi-phase trial. It is recommended that the table includes 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 7.2b is essentially the same as Table 7.2a except it is an example of when grouping reasons isn't 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. Although 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 more specific documentation of the true reason.

Table 7.3 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. As discussed in Section 6.4.1, a decision is required as to

whether the medications will be listed as brand names, generic names, or some other coded name.

Table 7.4 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.

Table 7.5 is a recommended display for medications of interest sorted by the medication grouping of interest. It includes the individual medication along with the grouped medication (subjects still counted once) similar to adverse event preferred terms nested in System Organ Class. This table would only be needed if there is at least one medication grouping of interest.

Listing 7.2 is a recommended listing of all medications taken during the study. This listing allows easy access to additional information (e.g., dose) that may be of interest.

Table 7.1 Demographic Summary

Demographic Summary
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)

Demographic Parameter		Treatment A (N=XXX)	Treatment B (N=XXX)	Total (N=XXX)
Sex n(%)	n[a]	xx	xx	xx
	F	xx (x.x)	xx (x.x)	xx (x.x)
	M	xx (x.x)	xx (x.x)	xx (x.x)
	Missing	xx	xx	xx
Age (years)	n[a]	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx, xx	xx, xx	xx, xx
	Min, Max	xx, xx	xx, xx	xx, xx
	Missing	xx	xx	xx
Age Categories n(%)	n[a]	xx	xx	xx
	<65	xx (x.x)	xx (x.x)	xx (x.x)
	≥65 and <75	xx (x.x)	xx (x.x)	xx (x.x)
	≥75 and <85	xx (x.x)	xx (x.x)	xx (x.x)
	≥85	xx (x.x)	xx (x.x)	xx (x.x)
	Missing	xx	xx	xx
	≥65	xx (x.x)	xx (x.x)	xx (x.x)
	≥75	xx (x.x)	xx (x.x)	xx (x.x)
Race n(%)	n[a]	xx	xx	xx
	American Indian or Alaska Native	xx (x.x)	xx (x.x)	xx (x.x)
	Asian	xx (x.x)	xx (x.x)	xx (x.x)
	Black or African American	xx (x.x)	xx (x.x)	xx (x.x)
	Native Hawaiian or Other Pacific Islander	xx (x.x)	xx (x.x)	xx (x.x)
	White	xx (x.x)	xx (x.x)	xx (x.x)
	Multiple	xx (x.x)	xx (x.x)	xx (x.x)
	Missing	xx	xx	xx
Ethnicity n(%)	n[a]	xx	xx	xx
	Hispanic or Latino	xx (x.x)	xx (x.x)	xx (x.x)
	Not Hispanic or Latino	xx (x.x)	xx (x.x)	xx (x.x)
Weight (kg)	n[a]	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx, xx	xx, xx	xx, xx
	Min, Max	xx, xx	xx, xx	xx, xx
	Missing	xx	xx	xx

Country n(%)	**n[a]**	**xx**	**xx**	**xx**
	Country 1	**xx.x**	**xx.x**	**xx.x**
	Country 2	**xx.x**	**xx.x**	**xx.x**
	...			
	Country n	**xx.x**	**xx.x**	**xx.x**
	Missing	**xx**	**xx**	**xx**

Abbreviations: N = number of subjects in the population; Q1=25% Percentile; Q3= 75% Percentile; SD=Standard Deviation.
[a] Number of subjects with non-missing data, used as the denominator

Program Location: *program name*
Output Location: *output name*
Data Set Location: *data set name*

Figure 7.1 Patient Disposition

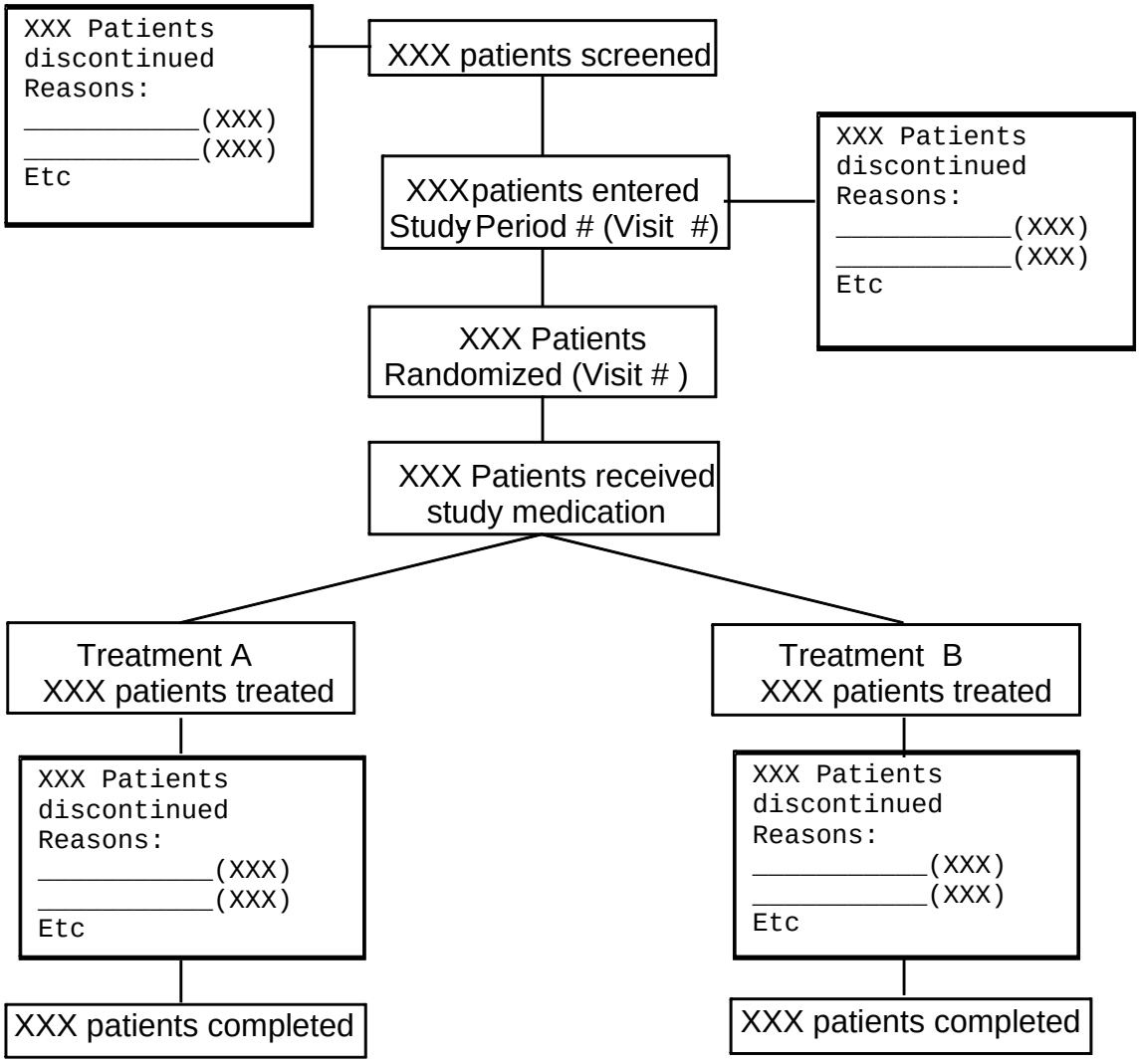

Table 7.2a Disposition table

Production/Test Data – Production/Test Mode

Subject Disposition
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)

Subject Disposition	Treatment A (N=XXX) n (%)	Treatment B (N=XXX) n (%)	Total (N=XXX) n (%)
Completed the study	xx(xx.x)	xx(xx.x)	xx(xx.x)
Discontinued	xx(xx.x)	xx(xx.x)	xx(xx.x)
Death or Adverse Event	xx(xx.x)	xx(xx.x)	xx(xx.x)
Death	xx(xx.x)	xx(xx.x)	xx(xx.x)
Adverse Event	xx(xx.x)	xx(xx.x)	xx(xx.x)
Lack of Efficacy-Related Reasons	xx(xx.x)	xx(xx.x)	xx(xx.x)
Lack of Efficacy	xx(xx.x)	xx(xx.x)	xx(xx.x)
Progressive Disease	xx(xx.x)	xx(xx.x)	xx(xx.x)
Disease Relapse	xx(xx.x)	xx(xx.x)	xx(xx.x)
Other Reasons	xx(xx.x)	xx(xx.x)	xx(xx.x)
Lost to Follow-up	xx(xx.x)	xx(xx.x)	xx(xx.x)
Non-compliance with Study Drug	xx(xx.x)	xx(xx.x)	xx(xx.x)
Pregnancy	xx(xx.x)	xx(xx.x)	xx(xx.x)
Protocol Violation	xx(xx.x)	xx(xx.x)	xx(xx.x)
Physician Decision	xx(xx.x)	xx(xx.x)	xx(xx.x)
Withdrawal by Subject	xx(xx.x)	xx(xx.x)	xx(xx.x)
Withdrawal by Parent/Guardian	xx(xx.x)	xx(xx.x)	xx(xx.x)
Recovery	xx(xx.x)	xx(xx.x)	xx(xx.x)
Technical Problems	xx(xx.x)	xx(xx.x)	xx(xx.x)
Other	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.
%= Percentage of patients with N as the denominator.

Program Location: *program name*
Output Location: *output name*
Data Set Location: *data set name*

Table 7.2b Disposition table

Production/Test Data – Production/Test Mode

Subject Disposition
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)

Subject Disposition	Treatment A (N=XXX) n (%)	Treatment B (N=XXX) n (%)	Total (N=XXX) n (%)
Completed the study	xx(xx.x)	xx(xx.x)	xx(xx.x)
Discontinued	xx(xx.x)	xx(xx.x)	xx(xx.x)
Death	xx(xx.x)	xx(xx.x)	xx(xx.x)
Adverse Event	xx(xx.x)	xx(xx.x)	xx(xx.x)
Lack of Efficacy	xx(xx.x)	xx(xx.x)	xx(xx.x)
Lost to Follow-up	xx(xx.x)	xx(xx.x)	xx(xx.x)
Non-compliance with Study Drug	xx(xx.x)	xx(xx.x)	xx(xx.x)
Pregnancy	xx(xx.x)	xx(xx.x)	xx(xx.x)
Protocol Violation	xx(xx.x)	xx(xx.x)	xx(xx.x)
Physician Decision	xx(xx.x)	xx(xx.x)	xx(xx.x)
Withdrawal by Subject	xx(xx.x)	xx(xx.x)	xx(xx.x)
Withdrawal by Parent/Guardian	xx(xx.x)	xx(xx.x)	xx(xx.x)
Recovery	xx(xx.x)	xx(xx.x)	xx(xx.x)
Technical Problems	xx(xx.x)	xx(xx.x)	xx(xx.x)
Other	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.
%= Percentage of patients with N as the denominator.

Program Location: *program name*
Output Location: *output name*
Data Set Location: *data set name*

Listing 7.1 Subjects who Discontinue due to Physician Decision, Withdrawal by Subject, Withdrawal by Parent/Guardian, or Other

Production/Test Data – Production/Test Mode

<Enrolled / Randomized> Population – Subjects who discontinue 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: Treatment A

Subject ID	Reason for Discontinuation	Textual Reason
101001	YYYY	xxxxxx
101004	YYYY	xxxxxx
ETC		

Program Location: *program name*
Output Location*: output name*
Data Set Location: *data set name*

Table 7.3 Prior Medications

Production/Test Data – Production/Test Mode

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

Prior Medication	Treatment A (N = XXX) n (%)	Treatment B (N = XXX) n (%)	Total (N = XXX) n (%)
Patients with >=1 Prior Medication	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prior Med 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prior Med 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC			

Abbreviations: N = total number of subjects in the population; n = number of subjects the specified category.
%= Percentage of patients with N as the denominator.

Program Location: *program name*
Output Location: *output name*
Data Set Location: *data set name*

Table 7.4 Concomitant Medication

Production/Test Data – Production/Test Mode

Concomitant Medication
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)

Concomitant Medication	Treatment A (N = XXX) n (%)	Treatment B (N = XXX) n (%)	Total (N = XXX) n (%)
Patients with >=1 Concomitant Therapy	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Med 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Med 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC			

Abbreviations: N = total number of subjects in the population; n = number of subjects the specified category.
%= Percentage of patients with N as the denominator.

Program Location: *program name*
Output Location: *output name*
Data Set Location: *data set name*

Table 7.5 Concomitant Medication within Classes of Interest

Production/Test Data – Production/Test Mode

Concomitant Medication
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)

Concomitant Medication	Treatment A (N = XXX) n (%)	Treatment B (N = XXX) n (%)	Total (N = XXX) n (%)
Patients with >=1 Concomitant Therapy	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Med class name	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Med 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Med 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc			
Concomitant Med class name	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Med 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Concomitant Med 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC			

Abbreviations: N = total number of subjects in the population; n = number of subjects the specified category.
%= Percentage of patients with N as the denominator.

Program Location: *program name*
Output Location: output name
Data Set Location: *data set name*

Listing 7.2 Listing of Medications

Production/Test Data – Production/Test Mode

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)

Treatment: Treatment A

Subject ID	Medication	ATC term(s)	Generic 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.

Program Location: *program name*
Output Location: output name
Data Set Location: *data set name*

7.2. Discussion

The recommended demographics table (Table 7.1) and the recommended disposition tables (Tables 7.2a and 7.2b) were developed with little controversy. There was some discussion on whether to recommend the listing (Listing 7.1), as it would be new for most companies. However, given the increased scrutiny on missing data, the listing is recommended.

Developing recommendations for medications was much more interesting! From the reviewed guidelines, there are no requirements to provide a summary table for prior or concomitant medications. ICH E3 includes a recommendation that all concomitant medications (along with other data) for all individual patients randomized be presented in by-patient tabular listings in an appendix. However, this recommendation might be considered unnecessary when patient data is provided to a regulatory agency.

Consideration was given to not recommend any summary and listing table for prior and concomitant medications. Having the data available for possible adverse reaction exploration and/or individual case assessment could be sufficient. However, despite the lack of requirements for a summary table for medications, such tables are very useful for gaining an understanding of the population under study and could facilitate the identification of topics that may deserve further evaluation. Thus, simple summary tables by treatment are recommended. To further explore the possibility of drug-drug interactions, the by-subject listing can provide more detail about all medications the subject has taken.

Consideration was also given whether to recommend a summary table that utilizes the different ATC categorizations (Table 12.1). However, given the complexities of getting to correct and useful categorizations, such a complex summary was considered unnecessary for general summary purposes. If the review of the simpler summary identifies something that would need further evaluation, ATC categorizations may end up being useful in the ad-hoc context.

8. Tables and Figures for Integrated Summaries

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 participants, interventions, and outcomes. Methodological diversity refers to differences in how the studies were executed, including study design (for example, 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.

In general, many of the TFLs recommended in section 7.1 of this white paper can be adapted for the integrated summaries.

If the team does decide to include p-values, the Cochran-Mantel-Haenszel (CMH) general association test (or row mean scores as appropriate) stratified by study is recommended for categorical variables, and ANOVA with study as a blocking factor is recommended for continuous variables.

9. Example SAP Language

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 to <75, ≥75 to <85, ≥85, ≥65 and ≥75. For continuous variables, the following statistics will be provided: the number of patients, mean, standard deviation, minimum, maximum, median, 25^{th} and 75^{th} percentile. For categorical variables, percentages will be calculated using the number of patients with non-missing data for the specific variable.

Reasons for 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 reaons (lack of efficacy, progressive disease, and disease relapse) will be provided.

Patient disposition will be displayed in a flowchart showing number of patients screened, entered, randomized, received medication by treatment, discontinued across all study periods by treatment, and completed by treatment.

The proportions of patients who received previous therapy will be summarized by WHO Drug Dictionary preferred names. The proportions of patients 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 WHO Drug Dictionary preferred names.

10. References

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National Cancer Institute. Find text: CDISC's Study Data Tabulation Model (SDTM) and download codelist file in e.g. excel. or use this link: Index of /ftp1/CDISC

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12. Appendix

Table 12.1 Summary of Concomitant Medications by ATC Code

Production/Test Data – Production/Test Mode

Concomitant Medication
Summary and Analysis 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)

ATC Level	Comparator N=xxx n (%)	Treatment N=xxx n (%)	OR*a
ATC Level 1 term 1	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 2 term 1	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 3 term 1	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 4 term 1	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 4 term 2	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
< *more terms* >	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 4 term n	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 3 term 2	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 4 term 1	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 4 term 2	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
<*more terms*>	xx(xx.x)	xx(xx.x)	xx.xx
ATC Level 4 term n	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx
ConMed Name	xx(xx.x)	xx(xx.x)	xx.xx

Abbreviations: N = number of evaluable subjects in the population; n = number of subjects with the medication; OR = Mantel-Haenszel odds ratio; add more as needed (alphabetically).

Program Location: ***program name***
Output Location: ***output name***
Data Set Location: ***data set name***