

A Survey of Clinical Trials Regulations and Their Impact on CDM

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1 Introduction

CDM is part of the regulated industry of drug development, but very little in the regulations specifically references data management. Data managers must read between the lines of the regulations to understand their part in meeting the expectations. The tables below are an overview of segments of regulations that impact data management, and provide brief explanations and/or interpretations of the wording. The information is organized by data domain, and covers only safety data. There are some guidances for specific diseases, and if the data manager is working in one of those therapy areas they should read those guidances. Note that the information in this article is intended to assist data managers, but as there are often several ways of interpreting the guidances this information should not be taken as an official or

FDA/ICH-approved interpretation. Data managers should always consult with their regulatory and QA colleagues for their own company-specific views.

Sources:

- FDA Guidances finalized as of 31 March 2006
(<http://www.fda.gov/opacom/morechoices/industry/guidedc.htm>)
- Code of Federal Regulations (CFR)
(<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>)
- ICH Harmonized Efficacy Guidelines finalized as of 31 March 2006
(www.ich.org)

Scope:

- Includes information on the collection, analysis and reporting of safety data
- Includes information commonly found in clinical trials databases, and not the extended information required for expedited adverse event reporting.
- Includes descriptions of the kinds of information present in the regulations, but does not list all the individual data fields.
- Excludes references to:
 - appropriate protocol designs for enabling safety assessments
 - safety reporting for post-marketing trials, post-marketing spontaneous reports and pharmacovigilance. Focus is primarily on pre-marketing information.

Key:

- Source: defines the regulatory body that issued the regulation or guidelines.
- Regulation/Guideline: the reference number and title of the regulation or guidelines.
- Description/Wording: provides an interpretation of the intent of the regulations/guidelines as it applies to the collection, analysis and reporting of clinical data, as well as specific wording from the guidelines where useful. Generally the reader should reference the original document for details. Wording in italics contains some suggestions for the implications of the regulation on data management practices. It is not exhaustive, and data managers should take these insights and apply them broadly.

2 Adverse Events

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E2A: Clinical Safety Data Management: Definitions And Standards For Expedited Reporting	Section II: Provides definitions for terms commonly used in safety data reporting, such as adverse event, serious adverse event and expectedness.
ICH	E3: Structure and Content of Clinical Study Reports	References to AE analysis and reporting appear in several sections of E3. Section 12.2 addresses the requirements most specifically.

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<ul style="list-style-type: none"> • Section 9: discusses rating AEs in terms of severity or relationship to drug. It also states that the report should define how consistency in applying the ratings was achieved between sites. <i>Be clear in defining the severity and relationship categories, and include the definitions in CRF completion guidelines.</i> • Section 12.2: provides a fairly detailed description of the kinds of safety summaries that must be conducted for AEs. These include summarization of AEs by body system, by intensity if used, by relationship to treatment if collected, and by treatment emergence. Summaries should include lab findings and vital signs changes identified as AEs. Even if AEs are categorized by relationship and/or treatment emergence, all AEs should be included in the summaries. <i>Although E3 does not require that relationship to study drug be captured, the EU Directive on AEs (April 2006) does require it. There must be a way to determine treatment emergence (both for increases in severity and in frequency). Labs and vital signs must be mergeable with AEs data, or somehow accessible.</i> • Section 12.2.3: describes the general analysis approach for AEs, including examination of relationship to dosage level if that seems appropriate. <i>This implies that the data must include dosage dates and levels, and AE dates and severities.</i> • Section 12.2.4: provides a list of fields that must be included in AE listings (i.e., that need to be collected). These include typical AE fields, as well as study drug treatment data and concomitant treatment data. Note that while the FDA does not require <u>listings</u> of AE data if AE data have been provided electronically, ICH guidelines do request these. • Section 12.3: Discusses the display of Deaths & other Serious Adverse Events (SAEs); they should be split out and discussed separately, in the report, but essentially the same data are required for display. Additionally, it requires that “significant” AEs be split out, i.e., AEs that were not serious, but required some significant concomitant therapy or intervention. <i>This implies that AEs requiring significant concomitant treatment (either pharmacological or non-pharmacological) be specifically identifiable.</i>
ICH	E9: Statistical Principles for Clinical Trials	<p>This guidelines in fairly general in its observations, but provides some insight into regulatory expectations.</p> <ul style="list-style-type: none"> • Section VI: Evaluation of Safety and Tolerability: Contains considerable discussion about appropriate approaches to the analysis and reporting of safety data. • Section VII: Reporting – provides a supplement to the info contained in E3.
FDA	Guidance for Industry: Premarketing Risk Assessment	Provides guidance on approaches to evaluating a drug's risk profile. While much of it focuses on pooled data and guidelines for pooling data, there are implications for

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<p>individual studies, particularly in terms of coding, and the analysis of temporal relationships of drugs and AEs.</p> <ul style="list-style-type: none"> • Section VI.A.1., Accuracy of Coding: provides recommendations around coding AEs, and ensuring appropriate coding. • Section VI.B, Analyzing Temporal or Other Associations: discusses the importance of being able to determine the timing of AEs both relative to treatment dates as well as to length of exposure to treatment. <i>This emphasizes the need to capture complete and accurate event dates.</i> • Section VI.G, Long-term Follow-up: discusses the need to determine what an appropriate follow-up period is for AE collection, and suggests that this should be discussed with regulatory authorities, potentially during end-of-Phase-2 meetings. <i>This should drive the cut-off point for collecting AEs for a study, and how long the database needs to remain open for adding AEs after the study is completed.</i> • Section VI.H, Important Aspects of Data Presentation: this is a supplement to the ICH E3 guidelines, and it covers additional analyses to be considered. Particularly, it states that for subjects who died during the study, the official CRF should contain copies of hospital records, autopsy reports, biopsy results, and any other pertinent information. This doesn't necessarily mean this information must be specifically collected on sponsor-generated CRFs, but that copies of this information should be stored with the rest of the subject data, and be appropriately indexed and referenced.
ICH	E2A Clinical Safety Data Management : Definitions and Standards for Expedited Reporting	<ul style="list-style-type: none"> • Provides definitions for terms commonly used in safety data reporting, such as adverse event, serious adverse event and expectedness • Defines processes for expedited reporting, including what must be reported and how to determine reporting timeframe • Outlines assessing safety during blinded treatment, associated with placebo treatment, and post-study events • Does not go into any detail around individual data points required, although contains some inferences about what SAE narratives must include
ICH	E2B (M) Maintenance Of The ICH Guideline On Clinical Safety Data Management : Data Elements For Transmission Of Individual Case Safety Reports	<p>This document lists data points that must be transmitted when sending expedited AE reports. <i>While these are often handled by the Regulatory departments in companies, there should be discussions with CDM to determine the relationship of this information to the clinical database.</i> <u>NB: as of Mar 2006 there is a new version of this document out for review (E2B (R3)). It contains clarifications and improvements. Its expected finalization date is unknown.</u></p>
ICH	E6 (R1): Good Clinical Practice	<ul style="list-style-type: none"> • 4.11: Investigator responsibilities for reporting safety issues to sponsors, specifically SAEs, Lab AEs and

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<p>AEs of special interest in a particular protocol</p> <ul style="list-style-type: none"> • Most of the rest of GCPs have more to do with actions around data, rather than the data themselves. • 5.16: Sponsor responsibilities for ongoing review of safety information; notification of investigators. • 5.17.1 and 5.17.2: Spell out the sponsor's regulatory responsibility to report all serious and unexpected AEs to IRBs, investigators and regulatory authorities in accordance with ICH E2A, Clinical Safety Data Management • 5.17.3: Sponsor responsibilities of periodic safety updates to regulatory authorities.
ICH	E11: Clinical Investigation of Medicinal Products in the Pediatric Population	Describes regulatory expectations in pediatric studies. Primary importance is to indicate applicability of E2 and E6 to pediatric studies as well as other populations.
FDA	Guidance For Industry: Content And Format For Pediatric Use Supplements (1996)	Document provides guidance on what information must be submitted to the FDA for a supplemental NDA to cover pediatric use.
FDA	Guideline for the Study of Drugs Likely to be Used in the Elderly (1989)	Describes the need for analyses of AEs and efficacy in elderly populations.
FDA	21 CFR Part 312 – Investigational New Drug Application	312.33.3b Section 1 through 4: Annual reports related to safety information. <i>May require the production of interim safety summaries and reports.</i>

2.1 Disease-Specific AE Reporting

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E12A: Principles for Clinical Evaluation of New Antihypertensive Drugs	Describes particular considerations that must be observed when studying new antihypertensive drugs
FDA	Guidance for Industry Cancer Drug and Biological Products - Clinical Data in Marketing Applications	Describes the expected data to be collected for cancer drug applications. There is a section specific to toxicity, which describes when to collect toxicity, but does not specify exactly what data to collect. There is a theoretical example of a drug development history that may be helpful to teams designing oncology studies.
FDA	Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)	<p>From the Introduction: <i>This guidance is intended to assist developers of drugs, biological products, and medical devices intended for the treatment of rheumatoid arthritis (RA). The document discusses the types of label claims that can be considered for such products and provides guidance on the clinical development programs to support those claims.</i></p> <p>There are other sections that provide information on how to approach safety assessments in RA trials, but they have to do more with study designs, subject populations and types of safety assessments rather than data-specific recommendations.</p>

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
FDA	Guidance for Industry: Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments	Extensive discussion of the recommended approach to assessing safety in Medical Imaging Drug and Biologic Products.
FDA	Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers	Provides lists of AEs and defines how to grade them with respect to toxicity for vaccine trials in healthy volunteers. <u>This guidance is out for industry review, and has not been finalized. Regardless, it offers useful classifications.</u>

3 Compliance

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3, Structure and Content of Clinical Study Reports	<p>Section 12.1, Extent of Exposure: specifies that the CSR should characterize each subject population with respect to the duration of exposure, the dose, and, if available, the drug concentration (i.e., C_{max}). This applies to exposure to placebo and active control as well as study medication.</p> <p>This verbiage is virtually identical to E1, Extent of Population Exposure to Assess Clinical Safety.</p> <p>In order to assess Exposure appropriately, compliance must be gauged.</p>
ICH	E4, Dose-response Information to Support a Drug Registration	<p>Discusses various trial designs and various ways of assessing exposure and its relationship to efficacy and to safety issues. The implication of this guidance to this DLP is that the DLP (and therefore the study) should collect the right data to allow for fairly specific and detailed analyses of exposure, dose, duration and concentration.</p> <p><i>It is important to note that compliance is not the same as drug accountability. Compliance speaks to whether the subject took the study medication as required by the protocol. Drug accountability means the ability to account for all the study medication, whether or not the subject took it. Generally, drug accountability records are a poor way of assessing compliance.</i></p>

4 Concomitant Non-Drug Treatments

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3, Structure and Content of Clinical Study Reports	<ul style="list-style-type: none"> Section 9.4.7., Prior and Concomitant Therapy - This part of the guideline states that allowed prior and concomitant drugs <i>or therapies</i> must be discussed in the report, and an assessment of their potential impact on study endpoints must be addressed. Section 12, Safety Evaluation - In the introduction to this section, the guideline states that "Significant Adverse

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<p>Events” (as distinct from SAEs) must be identified. This is defined as AEs that resulted in an intervention such as dose withdrawal or reduction, or significant additional concomitant therapy.</p> <ul style="list-style-type: none"> • Section 12.2.4., Listing of Adverse Events by Subject - In the section that describes the information that must be presented in by-subject adverse events listings, fields listed include “concomitant treatment during study” and the list of example answers for “Action Taken” includes “specific treatment instituted.” • Section 12.3.1.3, Other Significant Adverse Events - States that significant AEs, other than those listed as SAEs, must be listed as well.

5 Death

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3, Structure and content of a Clinical Study Report	Sections 12.3.1, 12.3.2 and 12.3.3: Deaths are to be analyzed and presented separately from other data. Deaths occurring both during the study as well as during the post treatment follow-up period are to be included. The guideline includes a description of what the subject narrative must discuss, including a list of data points. In the list of appendices, the guidelines indicate that CRFs for subjects who died must be submitted. <i>This implies that death data must be either collected for all studies on CRFs or on the serious AE collection instruments.</i>
ICH	E2A, Clinical Safety Data Management : Definitions and Standards for Expedited Reporting, Attachment 1, Section 4, page 10 (Nov 1994)	The description of the information required for expedited reporting of serious adverse events outlines further information that may be required to characterize deaths, including items such as allergy, drug or alcohol abuse; family history; findings from special investigations. An autopsy or other post mortem findings must be included when available. This may have implications for data to be collected in every study.
ICH	E6 Consolidated Good Clinical Practices	<ul style="list-style-type: none"> • Section 1.50 - Definition of SAE • Section 4.11.3 - Investigator responsibilities in regards to death reports • Section 5.16 - Sponsor responsibilities for safety review
FDA	Reviewer Guidance Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review	<p>Section 7.1.1 - This document instructs FDA reviewers on how to review and assess NDAs. It provides quite a bit more detail than ICH E3 on what specifically reviewers must look for in an application, and how they must present the conclusions. This can provide valuable insight into what data and analyses must be included.</p> <ul style="list-style-type: none"> • It lists the criteria for whether a death must be included in an evaluation or not. • It describes how an overall mortality analysis and display must be presented. • The reviewer will assess the sponsor’s approach to

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<p>determining what deaths to include, how they were coded and how drug-relatedness was determined.</p> <ul style="list-style-type: none"> • There is also a long list of items that the reviewer will assess themselves in examining deaths and their relationship to study drug. • An example of a listing for death information is provided, and a sample layout for a mortality summary is also included.
CFR	21 CFR 312.32 IND Safety reports	Definition(s) of SAEs, including Death, and expedited reporting information.
CFR	21 CFR 312.33 - Annual Reports	Primarily section 312.33 (b) (3) - summary information referring to death listings.
CFR	21 CFR 314.80 - Post marketing reporting of adverse drug experiences	Definition of SAE.
EC	European Commission: Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, ENTR/CT3 April 2006.	Presents extensive information on expedited reporting of serious AEs. It is very similar to ICH E2A and E2B, although it provides somewhat more specificity in places. It doesn't define requirements for any additional data, but rather clarifies roles and responsibilities, and timelines for reporting.

6 Demography

General Notes:

- Demographic data are loosely defined in the regulations and guidances, and lists of examples frequently contain elements of prior conditions. This document uses the narrow definition of demography as outlined by CDISC, i.e., age (date of birth), sex, race and ethnicity, excluding drug treatment variables.

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
FDA	Guidance for Industry Collection of Race and Ethnicity Data in Clinical Trials	<ul style="list-style-type: none"> • Outlines the FDA's approach to collecting and categorizing race and ethnicity data • Strong recommendation to collect self-reported race, with selections of "White" "Black" "Native American & Alaska native" "Hawaiian or Pacific Islander" "Other" "Other specify". • Other values can be added, but should be mapped back to these. • Ethnicity is optional, and when collected should be a separate field from race. As outlined, it is primarily for identifying Hispanic vs non-Hispanic <p><i>This regulation remains extremely US-centric, and studies conducted elsewhere may need to adapt codes as necessary. For studies where race and/or ethnicity are expected to be a focus of analysis, a more specific approach</i></p>

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<i>should be developed.</i>
FDA	Guideline For The Format And Content Of The Clinical And Statistical Sections Of An Application	The Format and Content of the Full Integrated Clinical and Statistical Report of a Controlled Clinical Study, Pg 74: The need to display sex, date of birth and race is referenced in numerous sections of this guidance, including listing safety information for each subject.
ICH	E.2.B, Clinical Safety Data Management Data Elements for Transmission of Individual Case Safety Reports	Part B.1: Defines demography information to be included with SAE reports
ICH	E3, Structure and Content of Clinical Study Reports	<ul style="list-style-type: none"> Section 11.2 - Demographic & other baseline characteristics, States that demography variables are usually expected. Sections 8, 12 & 14: various sections state requirement that key efficacy and safety data be presented broken down by various demographic variables
ICH	E5 Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data	Guidance discusses what kinds of factors may affect drug efficacy and sensitivity, and defines ethnicity vs race. It does not include any specifics about race, but provides a good summary of what characterizes ethnicity, how to consider it in evaluating a drug, and what it is most likely to affect.

7 ECG

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	<p>E14. The Clinical Evaluation Of QT/QTc Interval</p> <p>Also referred to as the EMEA QT/QTc guidance.</p>	<p><i>These quotes are taken directly from the guidance, and define the requirement for ECG data for general clinical trials</i></p> <p>2.2 The 'Thorough QT Study': The 'thorough QT/QTc study' would typically be conducted early in clinical development to provide maximum guidance for later trials, although the precise timing will depend on the specifics of the drug under development. It would usually not be the first study, as it is important to have basic clinical data for its design and conduct, including tolerability and pharmacokinetics. Some drugs might not be suitable for study in healthy volunteers because of issues related to tolerability (e.g., neuroleptic agents, chemotherapeutics).</p> <p>The results of the 'thorough QT/QTc study' will influence the amount of information collected in later stages of development:</p> <ul style="list-style-type: none"> A negative 'thorough QT/QTc study' will almost always allow the collection of on-therapy ECGs in accordance with the current practices in each therapeutic area to constitute sufficient evaluation during subsequent stages of drug development (see section 2.3); A positive 'thorough QT/QTc study' will almost always call for an expanded ECG safety evaluation during later stages of drug development (see section 2.3).

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<p>There could be very unusual cases in which the 'thorough QT/QTc study' is negative but the available nonclinical data are strongly positive (e.g., hERG positive at low concentrations and <i>in vivo</i> animal model results that are strongly positive).</p> <p>3. ANALYSIS OF ECG DATA FROM CLINICAL TRIALS Evaluation of the effects of a drug on the standard ECG intervals and waveforms is considered a fundamental component of the safety database of any new drug application.</p> <p>Regardless of the outcome of the 'thorough QT/QTc study', ECG changes recorded as adverse events should be pooled from all studies for analysis. ECG interval data from the 'thorough QT/QTc study' should only be pooled with subsequent trials of similar rigor with regard to ECG data collection and analysis, but should not be pooled with trials using less rigorous ECG collection. Standardization of ECG collection for similar studies within a clinical trial programmer will facilitate pooled analyses.</p> <p>The guidance also provides an outline of what the agencies expect with respect to the collection, presentation and analysis of ECGs.</p>

8 Eligibility

SOURCE	REGULATION/GUIDELINE	DESCRIPTION
ICH	E3 Structure and Content of a Clinical Study Report,	Section 9.3 Selection of Study Population - States that the criteria that subjects had to satisfy in order to enter the trial must be described (e.g., diagnostic criteria, demographic criteria), and any safety or other factors used to exclude subjects must be laid out and discussed. If there is reason to believe that there might have been systematic bias on the part of the investigator (e.g., not entering the sickest subjects), this must be described and its potential effects discussed.

9 Laboratory Data

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3, Structure of the Clinical Study Report	<ul style="list-style-type: none"> • Section 12, Safety Evaluation: Laboratory results are expected to be presented along with AEs, concomitant medications and other data that assess the basic safety profile of the drug • Section 12: laboratory results are one of the criteria for identifying significant non-serious AEs • Section 12.1, Extent of Exposure: CSR is expected to

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<p>present analyses of drug concentration in relationship to abnormal lab parameters, if seen</p> <ul style="list-style-type: none"> • Section 12.2.2.2, Adverse Events: significant lab abnormalities are expected to be presented along with other AEs • Section 16.1.10, Appendices, Study Information: states that there should be documentation of inter-laboratory standardization methods and quality assurance procedures if used
ICH	E9, Statistical Principals	<ul style="list-style-type: none"> • Section 6.2: states that lab values, along with vital signs and AEs, are expected to form the main body of evidence as to the safety of the drug

10 Medical History

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E2B Data Elements for Transmission of Individual Safety Case Reports	<p>Section B.1.7., Relevant Medical History: Medical history is listed as one of the elements that must be included in the evaluation and communication of expedited safety event reports. The User Guidance suggests that medical judgment must be used in determining what to record – focus on the findings that are at all likely to have a bearing on the event, rather than an exhaustive list of all observations. <i>This suggests that if there are specific medical history conditions of interest they might be best captured by asking specific questions, rather than relying on a general list.</i></p>
ICH	E3 Structure & Content of a Clinical Study Report	<ul style="list-style-type: none"> • Section 11.2, Demographic and Other Baseline Characteristics: Describes the information that must be included as part of the general characterization of comparative groups. It includes “relevant previous illness”, which refers to diseases other than that under study. This is another term for “Medical History.” • Section 11.4.5, Drug-Drug and Drug-Disease Interactions: states that relationships between subject response and prior illness must be described. This does not necessarily imply that medical history must capture an exhaustive list of prior conditions; it may be appropriate to focus on particular conditions or classes of condition. • Section 12.3.2. Narrative of Deaths, Serious AEs: “previous illness” is an element that must be addressed in characterizing serious adverse events.
ICH	E6 Consolidated Good Clinical Practices	<p>Section 8.3.13 Source documents - To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject.</p>

11 Pharmacokinetic Analysis

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E8, General Considerations for Clinical Trials	Section 3.1.3.1.; Phase 1 Trials: discusses the primary role that clinical pharmacokinetics studies play in determining the fundamental dose response, safety and metabolic profile for new drugs. These studies are generally associated with Phase 1, but can, and should, be conducted throughout the drug development period as additional information becomes available and further avenues of exploration become apparent.

12 Physical Examination

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3, Structure and Content of Clinical Study Reports	Section 12.5, Vital Signs, Physical Findings and Other Observations Related to Safety - Physical findings must be analyzed and displayed in the same manner as lab values. If any apparent relationship to dose effect or other response was observed, this must be discussed.
FDA	Premarketing Risk Assessment (2005)	Section VI H, Important Aspects of Data Presentation - States that physical exam findings are a useful part of the subject narratives associated with serious adverse events

13 Prior and Concomitant Medications

General Notes:

- One of the primary roles of concomitant medications data is to assist in the identification of significant non-serious adverse events (AEs), which are AEs for which significant therapy was instituted but that did not meet the criteria for “serious”. Significant AEs should be identified and discussed separately in the clinical study report. This implies an ability in the data to link the medications taken to the AE(s) for which they were taken.

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3, Structure and Content of Clinical Study Reports	<ul style="list-style-type: none"> • Section 9.4.7., Prior and Concomitant Therapy: This part of the guideline states that allowed prior and concomitant drugs or procedures should be discussed in the report, and an assessment of their potential impact on study endpoints should be addressed. • Section 10.1, Disposition of Subjects: States that it may be useful for the listings of subjects who discontinued the study early to include additional information, including concomitant medications • Section 10.2, Protocol Violations: Subjects who had protocol violations should be summarized in the report text by the type of violation. One type specifically mentioned is subjects who received excluded concomitant treatment.

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<ul style="list-style-type: none"> Section 11.2, Demographic and Other Baseline Characteristics and 11.4.3, Tabulation of Individual Response Data: Concomitant medications should be presented for all subjects in by-subject tabular listings. There are some specific recommendations for presentations in these sections. Section 12, Safety Evaluation: In the introduction to this section, the guideline states that “Significant Adverse Events” (as distinct from SAEs) should be identified. This is defined as AEs that resulted in an intervention such as dose withdrawal or reduction, or significant additional concomitant therapy, which is understood to include both non-pharmacological interventions and non-study medications. Section 12.2.4., Listing of Adverse Events by Subject: In the section that describes the information that should be presented in by-subject adverse events listings, fields listed include “concomitant treatment during study” and the list of example answers for “Action Taken” includes “specific treatment instituted.” Section 12.3.1.3, Other Significant Adverse Events: States that significant AEs, other than those listed as SAEs, should be listed as well. Section 12.6, Safety Conclusions: Overall safety discussion should pay particular attention to events requiring interventions, especially administration of concomitant medications
FDA	Guideline For The Format And Content Of The Clinical And Statistical Sections Of An Application	<p>There are a number of references to concomitant drugs and other therapies in this guideline. Below are the ones that most clearly impact decisions on the data to collect for a trial.</p> <ul style="list-style-type: none"> Section G.2.e, Integrated Efficacy, Subset analyses: concomitant medications are included in the list of parameters to be used for subset efficacy analyses H.4.i.3.b., Drug/Drug Interactions in the ISS: Specifically states that the concomitant therapies used in all studies should be listed, along with the numbers of subjects using each concomitant drug

14 Randomization

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3 Structure and Content of Clinical Study Reports	Sections 9.1, 9.2, 9.4.3, 9.4.6, 16.1.17 - Outlines the places in the CSR where Randomization should be addressed.
ICH	E6 Consolidated Good Clinical Practices	Sections 4.7, 6.4.3, 8.2.17, 8.2.18, 8.4.6 - Defines Randomization and requires that it be described in the Informed Consent. Requires that randomization procedures be followed, if defined for the study. Outlines the study-related documents in which Randomization must be

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		addressed (e.g., protocol, CSR)
ICH	E8 General Considerations for Clinical Trials,	Section 3.2.2.5. Methods to Minimise or Assess Bias - This section specifically states that the preferred method for assuring comparability of test groups and minimizing selection bias is randomization. It does not recommend any particular method.
ICH	E9, Statistical Principles for Clinical Trials	Section 2.3.2 - Provides recommendations for how to structure randomization in various trial designs
FDA	Guideline for the Format and Content of the Clinical and Statistical Sections of an Application	Section III.B.6.d. Method of Assigning Subjects to Treatment - Requires that any study not using randomization must specify what procedures were used to guard against systematic selection bias.
FDA	21 CFR 312.23 (6).iii.d	Protocol content must include a description of the design of the study including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators and analysts.

15 Study Drug

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3, Structure and Content of Clinical Study Reports	Section 12.1, Extent of Exposure: specifies that the CSR should characterize each subject population with respect to the duration of exposure, the dose, and, if available, the drug concentration (i.e., C_{max}). This applies to exposure to placebo and active control as well as test article. This verbiage is virtually identical to E1, Extent of Population Exposure to Assess Clinical Safety.
ICH	E4, Dose-response Information to Support a Drug Registration	Discusses various trial designs and various ways of assessing exposure and its relationship to efficacy and to safety issues. <i>The implication of this guidance is that the study should collect the right data to allow for fairly specific and detailed analyses of exposure, dose, duration and concentration.</i>

16 Subject Disposition

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E3, Structure and Content of Clinical Study Reports	Section 10.1 Disposition of Subjects: Specifically states the need to account for each subject randomized, and to summarize and discuss early withdrawals. An appendix provides an example of a flowchart showing the numbers of subjects who progressed through each phase of the study. <i>This implies that there must be a way of assessing how many screen failures there were (could bring screen fail CRFs in-house and enter), as well as specifically tracking the number of subjects completing each phase. Easiest</i>

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		<i>way to do this is usually to require that there be a CRF completed specifying the status of the subject at the termination of the phase.</i>

17 Substance Use

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E2A: Clinical Safety Data Management: Definitions And Standards For Expedited Reporting	Attachment 1, Section 4, Details of suspected adverse drug reaction: includes history of drug or alcohol abuse as information that may help in characterizing potential AEs.
ICH	E3: Clinical Study Report	Section 9.5.4, Drug Concentration Measurements: mentions that assessments of study drug concentrations should take into account characteristics that may affect it, such as concomitant medication/alcohol/caffeine/nicotine, among others.
ICH	E5: Acceptability of Foreign data	Refers to alcohol and tobacco usage as “extrinsic” ethnic factors that may be relevant when studying a drug in a different population.
ICH	E11: Pediatric Studies	Section 2.5.5 Adolescents (12 to 16-18 years (dependent on region)): encourages the examination of recreational use of drugs, alcohol and tobacco when doing studies in this population.

18 Treatment Blinding

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
ICH	E2A, Clinical Safety Data Management	Section III, D: Managing Blinded Therapy Cases: describes suggested approaches to breaking the blind and informing various involved parties as to the results. This particularly covers cases where there is an AE requiring expedited reporting, as not breaking the blind may result in reporting placebo-related events that may not be retracted for months or years. It suggests breaking the blind in these cases, but significantly restricting those who are informed.
ICH	E3, Structure and Content of a Clinical Study Report	Section 9.4.6, Blinding: states that the CSR must contain a description of what blinding was used, if any, and how it was designed and implemented, safeguards to ensure against accidental blind breaking, and processes for maintaining the blind when data review boards are used. Subjects for whom the blind was broken must be accounted for as a distinct population in the subject disposition displays.
ICH	E6, Consolidated Good Clinical Practices	Section 8, Essential Documents for the Conduct of a Clinical Trials: the list of essential documents includes one describing “decoding,” or breaking the blind, procedures.
ICH	E9 – Statistical Principles in Clinical Trials	Section 2.3.1, Blinding: Describes the need to protect the blind, and complete all changes to subject data and to analytical plans and procedures prior to breaking the study

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
		blind. Also states that all occurrences of the blind being broken for individual subjects, whether deliberately or by accident, must be described in the study report, along with a description of how the data were handled (e.g., the subject completely excluded from efficacy analyses, etc.)

19 Vital signs

SOURCE	REGULATION/GUIDELINE	DESCRIPTION/WORDING
FDA	Premarketing Risk Assessment	<ul style="list-style-type: none"> Section VI F, Rigorous Ascertainment of Reasons for Withdrawals from Studies: a detailed analysis of all withdrawals should be conducted, especially for those that withdrew due to changes that may not be captured as adverse events, such as ECGs or vital signs. Section VI H, Important Aspects of Data Presentation: States that adverse events important to a drug class should be comprehensively analyzed in the integrated summary of safety, along with relevant ancillary information such as vital signs.
FDA	MAPP (Manual of Policies and Procedures) for the Evaluation of NDAs	<ul style="list-style-type: none"> Section 7.2.5, Adequacy of Routine Clinical Testing: Vital Signs monitoring is considered to be one of the key indicators of whether good quality clinical care was provided to subjects in trials in an NDA.
ICH	E3, Structure and Content of Clinical Study Reports	<ul style="list-style-type: none"> Section 12.2.2., Display of Adverse Events: states that changes in vital signs considered relevant to adverse events should be displayed with the AEs. Section 12.5, Vital Signs, Physical Findings and Other Observations Related to Safety: Vital Signs should be analyzed and displayed in the same manner as lab values. If any apparent relationship to dose effect or other response was observed, this should be discussed.
ICH	E9 Statistical Principles for Clinical Trials	Section 6.2, Choice of Variables and Data Collection: Vital Signs are listed as one of the items that generally contribute to the body of evidence characterizing safety.