Clarity and **O**penness in **R**eporting: **E**3-based

An Open Access Resource to Support Authoring of Clinical Study Reports for Interventional Studies

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Preface to CORE Reference

What is CORE Reference?

The CORE (Clarity and Openness in Reporting: E3-based) Reference is a user manual to help medical writers navigate relevant guidelines as they create clinical study report (CSR) content relevant for today's studies.

CORE Reference comprises this Preface followed by the actual resource, which includes the following, distinguished from one another through the use of shading:

- ICH E3 guidance text. Text from the original ICH E3 guidance document is shown in unboxed grey shading.
- *ICH E3 Question & Answer 2012*-derived guidance text. Text from the ICH E3 Question & Answer 2012 guidance document is shown in italics with grey shading and a boxed outline.
- CORE Reference text. CORE Reference text is not shaded and not boxed.

All ICH E3 guidance text is either included as original wording; or is included as modified wording and the modification is explained; or is omitted, the omission is shown and the reason for the omission is explained.

All ICH E3 Question & Answer 2012-derived guidance text is included and explained.

In addition, relevant regional (EU and USA) regulatory guidances are integrated into the resource.

Further value-added insights, based on extensive collective experience, are included.

Rationale comments - in 'comment' format on the right hand side of each page - are used for explanation and clarification purposes.

A key explaining text shading and comments is included in the footer of each page of CORE Reference.

Where alternative presentations of the same information would work equally well in a CSR, they are shown with an explanation provided in the 'Rationale comments' to allow CSR authors to make informed authoring choices relevant for their particular study.

A separate mapping tool comparing ICH E3 sectional structure and CORE Reference sectional structure is also provided to support the utility of the CORE Reference.

Together, CORE Reference and the mapping tool constitute the user manual.

Why is CORE Reference needed?

Since ICH E3 was published in 1995, other guidance documents have been issued, including the ICH E3 Question & Answer guidance document in 2012. In addition, there has been heightened awareness of the importance of disclosure of clinical study results. The use of the CSR as a key source document to fulfil emerging obligations has resulted in a re-examination of how the ICH guidelines are applied in the preparation of CSRs in this new context. The dynamic regulatory and modern drug development environments create emerging reporting challenges.

Single CSR, Two Uses, Two Audiences

The CSR can be considered as a single document with two uses, each with a distinct purpose and audience:

- The 'primary use CSR' (the European Medicines Agency [EMA] term is scientific review version[1]) is a technical document for regulatory review and comprises full CSR text and all CSR appendices. The information reported must not constrain the review process.
- The 'secondary use CSR' (the EMA term is redacted clinical report[1]) is for public disclosure and comprises redacted CSR text and selected appendices. Sensitive information presented in the 'primary use CSR' is redacted in the 'secondary use CSR'.

CORE Reference makes content suggestions for the 'primary use CSR'. Comments are used to indicate individual CSR text portions that may potentially impact the 'secondary use CSR' and should therefore be considered for redaction in the 'secondary use CSR'.

It is assumed that data, including for example patient identification numbers, are not proactively anonymised. Over time, anonymisation techniques may allow appropriate proactive anonymisation of data that could be used to author 'primary use CSRs'. If proactively anonymised data is used to author the 'primary use CSR', then certain redactions may not be necessary in the 'secondary use CSR' for public disclosure.

When it is necessary to discuss any sensitive information, including individual subject level information in the text of the 'primary use CSR', the authors of CORE Reference recommend data and text presentations that maintain data meaning, remain in context AND conform to **current** standards for de-identifying data, because achievement of subject anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure. This approach brings efficiencies to the wider preparation of disclosure-ready documents.

[1] External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use. 2 March 2016. (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf [Accessed 04 April 2016]). Chapter 2, Section 3.3.1.9 states the cover letter including declaration will include 'Confirmation that the clinical reports submitted for scientific evaluation are the same as that submitted for publication…except for the redactions'.

This 'proactive' authoring approach is encouraged by EMA. Refer to 'External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use'. 2 March 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf (henceforth referred to as 'March 2016 EMA guidance on use of Policy 0070') Chapter 3, Section 5.1 'Data utility' states: 'EMA understands that in an initial phase redaction techniques are likely to be used by applicants/marketing authorisation holders (MAHs), taking into account that for a certain period, pharmaceutical companies will have to anonymise their data retrospectively (reactive data anonymisation), i.e. after the clinical report has already been submitted for scientific review. Importantly, redaction alone is more likely to decrease the clinical utility of the data compared to other techniques. Therefore, EMA is of the view that applicants/MAHs, after experience has been accumulated in the de-identification of clinical reports, should transition to other anonymisation techniques that are more favoured in order to optimise the clinical usefulness of the data published (proactive data anonymisation). Pharmaceutical companies are encouraged to use these anonymisation techniques as soon as possible, whilst ensuring data anonymisation is achieved'.

It is important to understand that although it is acceptable to disclose anonymised data that includes data that has been aggregated (i.e. tabular summary data), such data should be critically evaluated to determine the risk of de-anonymisation, considering the following, which may influence the risk of de-anonymisation from aggregated data[2], and may therefore influence the anonymisation technique:

- Is it possible to single out an individual?
- It is possible to link records relating to an individual?
- Can information be inferred concerning an individual?

It is expected that over time, more protected personal data (PPD) will be managed by anonymisation techniques that retain data utility prior to CSR authoring, resulting in fewer necessary redactions in the future.

Note that 'redaction' is the process of irreversibly blocking out sensitive information.

General Clarifications about CORE Reference

1. **CORE REFERENCE IS A USER MANUAL, NOT A TEMPLATE**: The CORE Reference presents suggestions and best practices that add value for medical writers creating ICH-compliant CSRs. **CORE Reference is not a template**. It offers suggestions for content, but does not mandate a particular sequence or organisation of the individual CSR sections. However, to allow easy mapping to the original ICH E3 guidance document and to avoid conflict with guidance documents that refer to ICH E3 sectional numbering, CORE Reference maintains the level 1 heading hierarchy of ICH E3. It remains at the author's

[2] Opinion 05/2014 on anonymisation techniques, adopted on 10 April 2014 by the Article 29 Data Protection Working Party. (http://ec.europa.eu/justice/data-protection/article-29/documentation/opinion-recommendation/files/2014/wp216_en.pdf [Accessed 04 April 2016]).

discretion to decide on the most appropriate CSR structure. Take, for example, ICH E3 'Section 15 References'. Logically, these should directly follow the CSR text as Section 14 content, so the order of ICH E3 Sections 14 and 15 would be switched. We have deliberately not switched these two sections in CORE Reference to avoiding conflicting with ICH E3, which might confound interpretation of other guidance documents that refer to 'ICH E3 Section 14 Tables and Figures'. This, of course, does not mean that in any given CSR the order should not be switched so that 'References' appear before 'Tables and Figures'. The CSR author may, with reference to the content guidance, place the content where he or she sees fit. Also consider that the CORE Reference suggested placement of sections cannot work in every conceivable situation, and is not 'the only way'. CSR authors should use their judgment, and above all, make sensible structuring choices, based on their particular study.

2. **LANGUAGE SELECTION**: Language of the collected data should not affect the language in the CSR. For example, UK English or US English should be used consistently within and across documents comprising a submission, or within a company. The exception is for the Medical Dictionary for Regulatory Activities i.e. MedDRA coding terms, which use UK English. It is recommended that these are not changed, even in a CSR written in US English.

3. **TO LINK OR NOT TO LINK**
   Appendices: Years may elapse between a CSR being finalised and subsequently integrated into a dossier with its CSR appendices. During this intervening period, the CSR text and appendices may not necessarily be electronically linked to one another. CORE Reference does not support using links from the CSR to appendix information if that information is necessary for comprehending the results in context, for example, inclusion and exclusion criteria should be placed directly in the text of the CSR and not via a link to the relevant protocol section.

   External documents: In the 'primary use CSR' for regulatory review, only non-active web addresses (i.e. not hyperlinked) supported by a digital object identifier (DOI), where possible, should be included, because active web links may become redundant or broken over time. This could compromise electronic upload of the submission dossier. Including DOIs in the 'primary use CSR' minimises the work that needs to be done in the 'secondary use CSR' for public disclosure. In the 'secondary use CSR', the non-active web addresses may be made into active web links (including the date the link was accessed). All references or publicly available guidelines in the 'secondary use CSR' should be supported by a DOI in the event that active web links become redundant over time. Note that users without institutional resources may not be able to access restricted articles.

4. **KEY TERMINOLOGY CHOICES**: In some cases, there are differences and discrepancies among the terminology used in authoritative sources in providing consistent concepts and definitions. This necessitates an explanation for use of some of the general terms used consistently in CORE Reference. Unless otherwise stated, CORE Reference terminology is per Clinical Data Interchange Standards

Consortium (CDISC) Clinical Research Glossary. Applied Clinical Trials, December 2011. (http://www.cdisc.org/system/files/all/standard_category/application/pdf/act1211_011_043_gr_glossary.pdf [Accessed 04 April 2016]).

In some cases, the term used is not in the CDISC glossary, in which case it is defined using other authoritative sources. In other cases, multiple definitions exist for a single intended meaning, in which case only one term is used consistently.

Key terms used in CORE Reference are presented below with reasons for their selection. Other choices may be equally acceptable in a CSR. The general rule is that language should be appropriate for the study in question and should be consistent within any given CSR.

a. **Study** or **trial**:
   - See ICH E6 Good Clinical Practice Guidelines, Section 1.12:
     - ICH E6: Guideline for Good Clinical Practice E6(R1) - Step 4, 10 June 1996 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf [Accessed 04 April 2016]).
     - Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) - Step 2, 11 June 2015 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf [Accessed 04 April 2016]).

     Both the original and addendum guidance state that study and trial are synonymous.
   - The European Clinical Trials Directive Amendment 291 dated 26 March 2014 (http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+AMD+A7-2013-0208+291-291+DOC+PDF+V0//EN [Accessed 04 April 2016]) clarifies the concept of clinical study of which the clinical trial is a category (see page 3 of the directive). The broad concept is that 'clinical study' includes the categories 'clinical trial' and 'non-interventional (observational) study'.
   - The "PASS" Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies, 26 September 2012 (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf [Accessed 04 April 2016]), uses 'study' only.

The use of the term 'study' as both the over-arching term and as a sub-term may cause interpretational difficulty. This simple diagram may aid interpretation:

TRIAL
Interventional
Pre-authorisation

STUDY
Non-interventional
Post-authorisation

Therefore mixed use of 'study' and 'trial' is acceptable in a typical CSR (i.e. interventional and pre-authorisation).

Note: The term 'study' is used in CORE Reference.

b. **Patient, subject, participant** etc:
See definitions in CDISC Clinical Research Glossary. Applied Clinical Trials, December 2011.
http://www.cdisc.org/system/files/all/standard_category/application/pdf/act1211_011_043_gr_glossary.pdf.

A patient is a person being treated. Until an investigational product is approved for an indication, 'subject' is a reasonable choice for use in a CSR (i.e. interventional and pre-authorisation). 'Patient' is also a reasonable choice except in early phase 'healthy-volunteer' studies. Note that vaccine trials use the term 'volunteers'. Alternatively, 'participant' may be used.

Note: The term 'subject' is used throughout CORE Reference.

c. **Investigational Product, study medication, study treatment, study drug** etc:
See definitions in CDISC Clinical Research Glossary. Applied Clinical Trials, December 2011.
http://www.cdisc.org/system/files/all/standard_category/application/pdf/act1211_011_043_gr_glossary.pdf.

The term used in CORE Reference is 'Investigational Product', selected from the CDISC glossary terms below, and by considering the definition of Investigational Medicinal Product in The European Commission's 'Definition of Investigational Medicinal Products (IMPs) and Non Investigational Medicinal Products (NIMPs)' (http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf [Accessed 04 April 2016]).

'Study medication' is not defined in CDISC Glossary, nor is it used in CORE Reference.

CDISC Glossary definitions:
Investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation (MA) when used or assembled (formulated or

packaged) in a way that is different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 Integrated Addendum to ICH E6[R1]: Guideline for Good Clinical Practice E6[R2] - Step 2, 11 June 2015 [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf], Section 1.33). Note: CDISC includes test articles in its definition of investigational products.

Study treatment: See intervention (modified from CDISC Glossary)

Therapeutic intervention: See intervention.

Intervention: The drug, device, therapy, or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study (for example, health-related quality of life, efficacy, safety, pharmacoeconomics). Synonyms: therapeutic intervention, medical product. See also: test articles; devices; drug product; medicinal product; combination product (refer to CDISC Glossary for definitions of these terms).

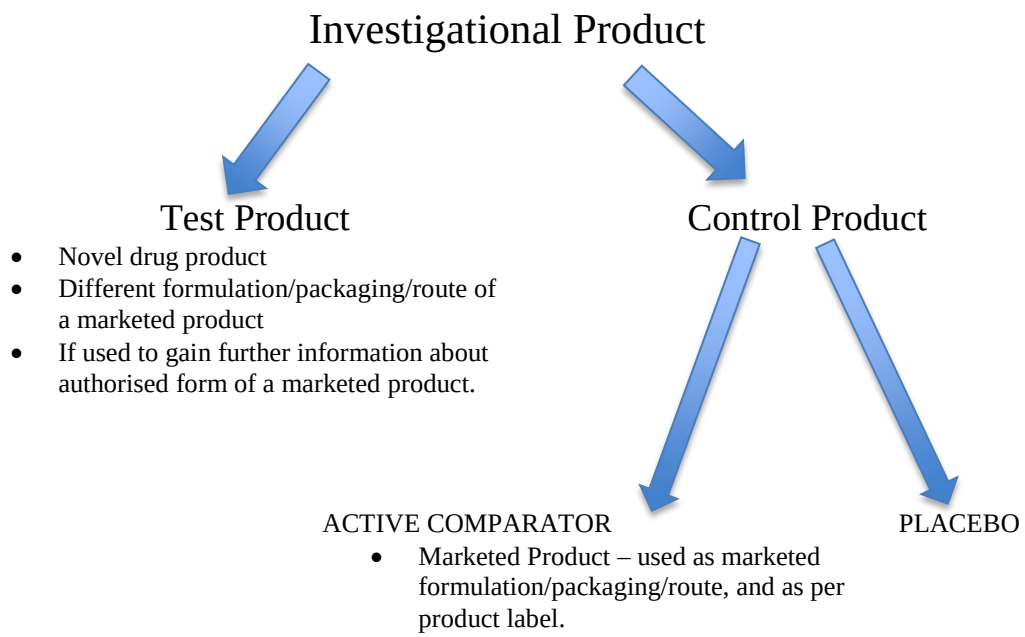
Medical product: See intervention.

Medicinal product: Synonym for therapeutic intervention, but usually a drug.

Drug:

1. Article other than food intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or intended to affect the structure or any function of the body. Not a device or a component, part, or accessory of a device.
2. Substance recognized by an official pharmacopeia or formulary, from Food and Drug Administration (FDA) Glossary of Terms. (http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm [Accessed 04 April 2016]).

This simple diagram may aid interpretation:



Note: The over-arching term 'Investigational Product' is used throughout CORE Reference unless it is necessary to make specific reference to any lower level term shown in the diagram above to aid understanding.

Other general terms are defined in CORE Reference at appropriate points in the text to aid usability. This includes the terms in the CORE Reference Terminology Page in Section 9.5.

d. Selected terms used in the context of **public disclosure**:
In some cases, there are differences and discrepancies among the terminology used in authoritative sources in providing consistent concepts and definitions around public disclosure of clinical-regulatory documents. This necessitates an explanation for language used in CORE Reference for such terms.

Where a definition is taken directly, or adapted from an external source to best represent the anticipated use of CORE Reference, the source is identified. Otherwise, the definition is attributable to the European Medical Writers Association (EMWA)-American Medical Writers Association (AMWA) Budapest Working Group.

Protected personal data (PPD) (also referred to as **personal protected information [PPI]**, and **individual personal data [IPD]**): Any information relating to an identified or identifiable natural person who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity (adapted from the Heads of Medicines Agencies [HMA]/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the MA application - release of information after the granting of an MA; http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf page 2 [Accessed 04 April 2016]), either from the data or from the data in conjunction with other information, for example: phone numbers, names, addresses, email addresses, regional location, age, gender, race/ethnicity, other demographic, or medical information3.

Commercially confidential information (CCI): Any information that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the owner of the information (adapted from EMA policy on publication of clinical data for medicinal products for human use. Policy 0070. 01 January 2015.

[3] Also see TransCelerate Biopharma Inc. Data De-identification and Anonymization of Individual Patient Data in Clinical Studies – A Model Approach (http://www.transceleratebiopharmainc.com/wp-content/uploads/2015/04/CDT-Data-Anonymization-Paper-FINAL.pdf, Appendix 1 Defining Protected Information [Accessed 04 April 2016]) and Pharmaceutical Users Software Exchange (PhUSE) De-Identification Working Group, "De-Identification Standards for CDISC SDTM 3.2," 2015 (http://www.phuse.eu/Data_Transparency_download.aspx [Accessed 04 April 2016)] for listed direct and quasi identifiers potentially found in clinical data, and that can facilitate identification of variables in clinical reports.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf [Accessed 04 April 2016]). This includes, for example, unprotected intellectual property and trade secrets.

Anonymised/de-identified data: Data in a form that does not identify individuals and where identification through its combination with other data is not likely to take place (March 2016 EMA guidance on use of Policy 0070. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf. Chapter 1, Section 3).

- **Anonymisation**: The process of rendering data into a form which does not identify individuals and where identification is not likely to take place (March 2016 EMA guidance on use of Policy 0070. Chapter 1, Section 3). Anonymisation can be performed using techniques such as:
  - **Masking**: The removal of values for variables which allow direct or indirect identification of an individual from the data (March 2016 EMA guidance on use of Policy 0070. Chapter 3, Section 5.3.2). Note that masking can sometimes be redaction or may involve data transformation.
  - **Redaction:** The process of irreversibly blocking out sensitive information.

Other anonymisation techniques include - but are not limited to - generalisation and randomisation. For further information see the March 2016 EMA guidance on use of Policy 0070.

The processes that result in anonymised/de-identified data may be applied to datasets as well as documents.

Note: Awareness comments are included in CORE Reference (PPD in blue text and CCI in red text) to indicate 'primary use CSR' text portions that should be considered for PPD or CCI impact in the 'secondary use CSR'.

References

CORE Reference aims to be globally acceptable. The following guidance documents were used to develop CORE Reference (Version 1.0, dated 03 May 2016).

Regulatory Resources

Where regulatory documents are region-specific, this is indicated:

1. ICH E6: Guideline for Good Clinical Practice E6(R1) - Step 4, 10 June 1996 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

2. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) - Step 2, 11 June 2015 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf.

Note that Step 4 [Final] is expected in November 2016. Awareness comments are included in CORE Reference **in green bold text**, pending finalisation of this ICH guidance document.

3. ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports E3. Step 4, 30 November 1995 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf. Accessed 04 April 2016.

4. ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers (R1), 6 July 2012 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf. Accessed 04 April 2016.

5. ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9. Step 4, 5 February 1998 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. Accessed 04 April 2016.

6. Final concept paper E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials, 22 October 2014 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf. Accessed 04 April 2016.

   Awareness comments are included in CORE Reference **in green bold text**, pending finalisation of this ICH guidance document.

7. CDISC Clinical Research Glossary. Applied Clinical Trials, December 2011. http://www.cdisc.org/system/files/all/standard_category/application/pdf/act1211_011_043_gr_glossary.pdf.

8. 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. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf. Accessed 04 April 2016.

This Regulation becomes applicable no earlier than 28 May 2016.

See items listed in Annex IV Section A: 'content of the summary of the results of the clinical trial'. Relevant items are included in the example CSR synopsis within CORE Reference to facilitate dual use for posting via the European Union (EU) portal. These items are tagged with explanatory comments and may be omitted for non-EU studies, or if the CSR synopsis is not intended for dual use.

Also see the European Commission home page for relevant general information: http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm. Accessed 04 April 2016.

This is region-specific (EU).

9. Study Data Tabulation Model (SDTM) data tabulations may be provided in place of US Archival Listings, which may mean that US Archival Listings may not be required in Appendix 16.4. This can also depend on drug and therapeutic area, and requires confirmation from your regulator. See FDA resources for data standards http://www.fda.gov/ForIndustry/DataStandards/. Accessed 04 April 2016.

   This is region-specific (US).

10. Committee for Medicinal Products for Human Use (CHMP) Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications. 23 June 2004 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003638.pdf. Accessed 04 April 2016.

    This is region-specific (EU).

11. European Medicines Agency pre-authorisation procedural advice for users of the centralized procedure, December 2015 EMA/339324/2007 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf. Accessed 04 April 2016.

    See '32. How are initial Marketing Authorisation Applications validated at the EMA: How to avoid most common Good Clinical Practice (GCP) validation issues'. This document details additional information on Appendix 16.1.4 requirements not described elsewhere.

    This is region-specific (EU).

12. FDA, CDER and CBER. Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications, August 1999 http://www.fda.gov/downloads/Drugs/Guidances/ucm072053.pdf. Accessed 04 April 2016.

    This US-specific guidance is widely adopted in practice in multiple regions.

Other relevant regulatory guidance documents, which may be country- or region-, therapeutic area- or study design-specific, should be followed for the reporting of individual studies.

Data Privacy

Selected relevant data privacy references:

1. Health Insurance Portability and Accountability Act (HIPAA) of 1996 (http://www.hhs.gov/ocr/privacy/index.html). Accessed on 04 April 2016.
   - Summary of the HIPAA Privacy Rule. http://www.hhs.gov/sites/default/files/privacysummary.pdf. Accessed 04 April 2016.
   - Summary of the HIPAA Security Rule. http://www.hhs.gov/hipaa/for-professionals/security/laws-regulations/index.html. Accessed 04 April 2016.
   - HIPAA Administrative Simplification, Regulation Text. Unofficial version, as amended through 26 March 2013. http://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/administrative/combined/hipaa-simplification-201303.pdf. Accessed 04 April 2016.

   These are region-specific (US).

2. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML. Accessed 04 April 2016.

   This is region-specific (EU).

3. WMA Declaration on Ethical Considerations Regarding Health Databases, October 2002 http://www.wma.net/en/30publications/10policies/d1/index.html. Accessed 04 April 2016.

4. Council of Europe Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data, 28 January 1981 http://www.coe.int/en/web/conventions/full-list/-/conventions/rms/0900001680078b37. Accessed 04 April 2016.

   This is region-specific (EU).

5. ISO Health Informatics - Classification of purposes for processing personal health information: ISO/TS 14265: 2011 http://www.iso.org/iso/catalogue_detail?csnumber=54547. Accessed 04 April 2016.

6. Health Canada - Privacy Act - Annual Report 2011-2012 http://www.hc-sc.gc.ca/ahc-asc/pubs/_atip-aiprp/2012priv-prot/index-eng.php. Accessed 04 April 2016.

This is country-specific (Canada).

Commercially Confidential Information

Selected relevant references describing and defining CCI; all are EU region-specific:

1. Principles to be applied for the deletion of commercially confidential information for the disclosure of EMEA documents (EMEA/45422/2006, 15 April 2007) http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004043.pdf. Accessed 04 April 2016.

   This document states "…the EMA will refrain from disclosing commercially confidential information when it might hurt the interest or, in other words, prejudice to an unreasonable degree the commercial interests, of individuals or companies concerned."

2. HMA/EMA recommendations on transparency. Recommendations on release of information with regard to new applications for medicinal products before and after opinion or decision on granting of a MA. November 2010 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099536.pdf. Accessed 04 April 2016.

   This document gives guidance on what regulators will consider to be CCI in an MA application.

3. HMA/EMA guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation (MA) application - release of information after the granting of a MA, 9 March 2012 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.

   This document gives guidance on what regulators will consider to be CCI and PPD in a marketing authorisation application (MAA).

4. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use). Policy 0043. 1 December 2010 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf. Accessed 04 April 2016.

5. European Medicines Agency policy on publication of clinical data for medicinal products for human use. Policy 0070. 1 January 2015 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf.

   Annex 3 titled 'Information contained in the sections of the clinical reports that may be considered CCI' - see table, column 2 (pages 19 and 20) for information that may be considered CCI in CSRs. The clinical information items listed that potentially contain CCI relate broadly to agreements relating to the protocol development between the Sponsor and regulators; exploratory objectives,

endpoints and variables (including biomarkers); information driving the sample size calculation and analytical methods of pharmacokinetic/pharmacodynamic determination.

These clinical items - summarised from the EMA guidance – are those that the authors of CORE Reference consider most relevant when writing a CSR. Refer to the guidance for full details.

Subsequently, in March 2016 the EMA released guidance on the implementation of Policy 0070. This guidance is shown below in 7.

6. Questions and answers on the European Medicines Agency Policy 0070 on publication of clinical data for medicinal products for human use http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/10/WC500174378.pdf. Accessed 04 April 2016.

7. External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use. 2 March 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf.

   This guidance is composed of procedural aspects, anonymisation of personal data and redaction of CCI.

   Chapter 4, Section 3.2 lists 'Information that EMA does not consider to be CCI'. See Section 3.2.3 Additional information the disclosure of which would be **in the public interest** – Rejection Code 03' – page 49/91.

EMA do not consider that information in the public domain is CCI. Refer to the guidance for full details.

This effectively removes from CCI the clinical information items listed in Policy 0070 as potentially containing CCI (see point 5 above). As a result of these CCI clarifications, these clinical information items are NOT flagged in CORE Reference.

Later in 2016, EMA is expected to announce the date of a webinar on the clinical data publication policy implementation.

This is region-specific (EU). See page 88 of 91: 'To be noted that the same CCI, PPD and publication principles will apply to EU as well as non-EU studies in the context of Policy 0070'.

Disclosure

Calls for responsible clinical trial data sharing:

1. Joint EFPIA-PhRMA Principles for Responsible Clinical Trial Data Sharing. Our Commitment to Patients and Researchers. 1 January 2014

http://transparency.efpia.eu/uploads/Modules/Documents/data-sharing-prin-final.pdf. Accessed 01 April 2016.

2. The National Academies of Sciences, Engineering and Medicine. Health and Medicine Division. Report: Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk. 14 January 2015 http://www.iom.edu/Reports/2015/Sharing-Clinical-Trial-Data.aspx. Accessed 04 April 2016.

3. World Health Organization Statement on Public Disclosure of Clinical Trial Results. http://www.who.int/ictrp/results/en/. Accessed 04 April 2016.

4. Taichman DB *et al*. Annals of Internal Medicine. Editorial: Sharing clinical trial data: A proposal from the International Committee of Medical Journal Editors. 26 Jan 2016. http://www.icmje.org/news-and-editorials/M15-2928-PAP.pdf. Accessed 04 April 2016.

   The International Committee of Medical Journal Editors (ICJME) proposal for manuscript publication requirements to help meet the obligation to responsibly share data generated by interventional clinical trials.

Current status of clinical trial data sharing:

1. Food and Drug Administration Amendments Act (FDAAA) of 2007. Public Law 110-85. 27 September 2007. http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf. Accessed 04 April 2016.

   This rule requires the registration and submission of summary results information to ClinicalTrials.gov for certain clinical trials of drugs (including biologic products) and devices. Summary results include four modules in tabular format: the numbers and flow of participants in the trial; baseline demographic and clinical characteristics of the participants according to study group; primary and secondary outcomes; and adverse events.

   This is region-specific (US).

2. Clinical Trials Registration and Results Submission – A proposed rule by the Health and Human Services Department on 11/21/2014. Federal Register. https://federalregister.gov/a/2014-26197. Accessed 04 April 2016.

   Health and Human Services Department proposes additional specificity to the FDAAA provisions and proposes further enhancements to the data for public disclosure. The public comment period ended on 23 March 2015. There is currently no timetable for amendment to the rule.

   This is region-specific (US).

3. Official Journal of the European Union. Commission Guideline: Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (2012/C 302/03).

http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf. Accessed 04 April 2016.

This guideline requires mandatory posting of clinical trial results using the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database.

This is region-specific (EU).

4. European Medicines Agency policy on publication of clinical data for medicinal products for human use. Policy 0070. 1 January 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf.

   This Policy mandates that publicly disclosed CSRs will include the following elements (identified per ICH E3 guideline numbering system):
   - CSR text portion (Sections 1–15),
   - Appendix 16.1.1 (protocol and protocol amendments),
   - Appendix 16.1.2 (sample case report form), and
   - Appendix 16.1.9 (documentation of statistical methods).

   Patient data listings (Appendix 16.2) will not be disclosed.

   Policy 0070 mandates that from 01 July 2015, CSRs from extension of indication and line extension applications are made publicly available, bringing them into alignment with CSRs in new MA applications, which were made publicly available from 01 January 2015.

   This is region-specific (EU).

5. External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use. 2 March 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf.

   This guidance is composed of procedural aspects, anonymisation of personal data and redaction of CCI.

   Chapter 2, Section 2.2 states that full redaction of narratives in the CSR for public disclosure is not allowed, and that ‘Case narratives should not be removed or redacted in full regardless of their location within the clinical reports (body of the report or listings). They should be instead anonymised. Regardless of the anonymisation technique used by the applicant/MAH, EMA cannot accept the redaction of the entire case narrative by default (as a rule). If, exceptionally, the entire case narrative needs to be redacted to ensure anonymisation, i.e. all identifiers (direct and indirect) need to be redacted, it has to be clearly justified in the anonymisation report. Likewise, patient level information referred to in the free text should not be redacted in full but instead anonymised’.

   Chapter 3: ‘External guidance on the anonymisation of clinical reports for the

purpose of publication in accordance with EMA Policy 0070' describes PPD items as:

- Subject-level data (will not be disclosed)
- Personal data of investigators, Sponsor staff and applicant/MAH staff – page 43/91
    - Sponsor signatory of CSR will be disclosed. Contact details and signature will not be disclosed
    - Name of investigators and their sites will be disclosed. Contact details will not be disclosed.

These items - summarised from the EMA guidance – are those that the authors of CORE Reference consider most relevant when writing a CSR. Refer to the EMA guidance for full details.

Later in 2016, EMA is expected to announce the date of a webinar on the clinical data publication policy implementation.

This is region-specific (EU). See page 88 of 91: 'To be noted that the same CCI, PPD and publication principles will apply to EU as well as non-EU studies in the context of Policy 0070'.

Public disclosure of clinical regulatory documents in Europe is a fast-developing area. Refer to EMA 'Clinical data publication' tab for the latest news: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa Accessed 04 April 2016
and EMA 'News and events' page:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid. Accessed 04 April 2016.

6. Health Canada. Regulatory Transparency and Openness: http://www.hc-sc.gc.ca/home-accueil/rto-tor/index-eng.php. Accessed 05 April 2016.
Regulatory Transparency and Openness Framework and Action Plan 2015-2018: http://www.hc-sc.gc.ca/home-accueil/rto-tor/index-eng.php#a1. Accessed 05 April 2016.

This is country-specific (Canada).

The data sharing requirements of the relevant region if not the US or EU, or country, should be followed.

Redaction

CORE Reference makes content suggestions for the 'primary use CSR'. Comments are used to indicate individual CSR text portions that may potentially impact the 'secondary use CSR' and should therefore be considered for redaction in the 'secondary use CSR'. See also 'Single CSR, Two Uses, Two Audiences'.

The redaction suggestions cannot be exhaustive, as items for redaction will also be company- and study-specific.

Where possible, segregating or appending information in the 'primary use CSR' that may require redaction in the 'secondary use CSR' is advised to minimise the number of text sections that potentially require redaction. It will be easier to redact or remove an entire section or annexed/appended section from a 'primary use CSR' than to redact information piecemeal within the report. A specific example of this relates to narratives. ICH E3 states that narratives may be placed in E3 Section 12.3.2 or in Section 14.3.3. The authors of CORE Reference suggest that narratives are placed in Section 14.3.3 for two reasons: a) to streamline processes across regions and b) to ensure that CSR text flow is not interrupted, particularly for studies with large numbers of narratives. Note that full redaction of narratives in the 'secondary use CSR' for public disclosure is not allowed in the EU as clarified in the March 2016 EMA guidance on use of Policy 0070. (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf).

Given the lag between 'primary use CSR' finalisation and 'secondary use CSR' public posting, standards for redaction may have changed between the final CSR date and the date of posting. Care must be taken to ensure that the 'secondary use CSR' follows relevant current standards at the time it is posted.

1. Hrynaszkiewicz I, Norton ML, Vickers AJ, Altman DG. Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers. Trials 2010;Jan29;11:9. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2825513/. Accessed 04 April 2016.

   This paper explains general issues of public sharing of certain data combinations that might result in identification of individual subjects.

2. Opinion 05/2014 on anonymisation techniques, adopted on 10 April 2014 by the Article 29 Data Protection Working Party. http://ec.europa.eu/justice/data-protection/article-29/documentation/opinion-recommendation/files/2014/wp216_en.pdf.

   Any data listings presented in the text of a publicly disclosed CSR should conform to current minimum standards for de-identifying data. The latest available standards are described in Opinion 05/2014. Opinion will inevitably be revised over time, and publicly disclosed data must take account of the evolving technological landscape and updated opinion on anonymisation techniques.

   This is region-specific (EU).

3. National Institutes of Health HIPAA Privacy Rule. http://privacyruleandresearch.nih.gov/pr_08.asp#8a. Accessed 04 April 2016.

   De-identified protected health information is defined in this rule, with 2 alternative approaches to de-identification: Safe Harbor Method and Expert Determination Method.

   This is region-specific (US).

4. TransCelerate BioPharma Inc. 'Clinical Study Reports Approach to Protection of Personal Data'. 28 August 2014. http://www.transceleratebiopharmainc.com/wp-content/uploads/2014/08/TransCelerate-CSR-Redaction-Approach.pdf. Accessed 04 April 2016.

   This document explains CCI and PPD, and removal and redaction of information, stating: 'The protection of CCI is a matter for individual companies, and further discussions and considerations are needed on this topic. In contrast, privacy considerations are not company specific and, because the global privacy landscape is diverse, they can be region or country specific… adjustments need to be made for local national privacy laws and regulations'.

   Note that in Section 5.1 of this document, full patient narratives are recommended to be removed. This is not allowed in the EU per March 2016 EMA guidance on use of Policy 0070.

5. TransCelerate BioPharma Inc. publication April 2015 'Data De-identification and Anonymization of Individual Patient Data in Clinical Studies – A Model Approach'
   http://www.transceleratebiopharmainc.com/wp-content/uploads/2015/04/CDT-Data-Anonymization-Paper-FINAL.pdf.

   This paper gives specific methods for handling sensitive data in datasets including identifiers, dates, date of birth, age, medical dictionaries and coding, free text verbatim fields, and sensitive information and low frequency events. Quality checks and process recommendations are also covered. ***Note that although this paper handles anonymisation for the purpose of data analysis, insights could be directly applicable to the CSR, in the case of narratives that need redaction***.

CORE Reference Technical Format Supports On Screen and Print Readability

Rationale Comment Anchoring and Positioning

Rationale comments are anchored to single blank spaces within the text. This avoids any word, phrase or passage of text being comment-highlighted (only the blank space is highlighted), but still allows a clear anchoring of the comment, without obscuring the text shading.

Each comment is positioned following the word, or the last word of the phrase, or the last word of the passage of text in need of the comment.

Where a comment follows an entire passage of text, the start and end points of the passage may be referenced within the comment itself if this adds clarity.

Unshaded Terms not Supported with a Rationale Comment

In CORE Reference, ICH E3 text is shaded and CORE Reference text is unshaded.

Consistent substitution of the following (shaded) ICH E3 terms with (unshaded) CORE Reference terms means that unshaded terms appear in text.

- ICH E3 uses both 'stud[y]/[ies]' and 'trial(s)'; CORE Reference uses 'stud[y]/[ies]'
- ICH E3 uses 'patients'; CORE Reference uses 'subjects'.

For these substituted terms only, the unshaded terms are not further supported by a Rationale comment, to support readability.

No Colour Shading

To support printing of CORE Reference with even the most basic printer hardware, text shading is deliberately monochrome. Colour shading and/or highlighting is not used in the body text.

Colour coding of text is limited to the Rationale comments, in order to indicate potential CCI and PPD items, and **non-final ICH guidance**. This minimal use of colour within CORE Reference should not unduly impact readability or printing.

Author Information

In May 2014, at the European Medical Writers Association (EMWA) Conference in Budapest, the lead author of CORE Reference and EMWA Vice President (SH) - convened the Budapest Working Group (BWG), a group of experts from the Medical Writing community, to address current controversies and limitations in the field of reporting clinical studies, and offer potential solutions. The BWG are the authors of CORE Reference.

The BWG comprises nine authors with between 17 and 40 years of experience in the pharmaceutical industry. Seven authors are either members of EMWA, AMWA or both organisations. The two remaining authors are members of Statisticians in the Pharmaceutical Industry (PSI). All nine authors gave their time and expertise to this project, voluntarily, in the belief that an open-access user manual to support clinical study reporting would benefit today's healthcare industry. Four authors have been (or currently are) officers of either AMWA or EMWA. Six authors have headed one or more Medical Writing departments. Six authors are regulatory medical writers who write and/or review CSRs in their professional lives, which extend to writing and/or reviewing the full range of clinical-regulatory documents contributing to the licensing of new medicines. Two authors individually contributed expertise for the entire body of work in the specialist areas of statistics and clinical pharmacology. Four authors contributed insight on transparency and public disclosure of clinical-regulatory documents, with one expert author taking overall responsibility for public disclosure considerations.

For publications and details of the Stakeholders involved in the development of CORE Reference, visit: www.core-reference.org.

CORE Reference has no official relationship with ICH or any regulatory/competent authority.

The authors accept no liability for CSRs written using CORE Reference.

At the time of publication, all URLs are functional. Use of web browsers that may not support URL functionality is outside the control of the authors of CORE Reference.


REFERENCE


EMWA
EUROPEAN
MEDICAL
WRITERS
ASSOCIATION


AMERICAN
MEDICAL WRITERS
ASSOCIATION
The Resource for Medical Communicators

1. TITLE PAGE

The title page should contain the following information:

- Study title
- Name of Test Product
- Indication studied (where available)
- If not apparent from the title, a brief (one to two sentences) description giving design (parallel, crossover, blinding, randomised), comparison (placebo, active, dose/response), duration, dose, and subject population
- Name of the Sponsor
- Protocol identification (code or number) and trial registry name(s) and number(s)
- Development phase of study
- Study initiation date (first subject enrolled, or any other verifiable definition)
- Date of early study termination, if any. In the case of studies where the Investigational Product development is terminated, indicate the date of Investigational Product termination
- Study completion date (last subject completed) or data cut-off date for long duration studies with interim reporting of data

Comment [A1]: Title Page does not need to be numbered Section 1 - see example title page below. Clinical study report (CSR) section numbering should be carefully considered from the outset to avoid possible conflict with numbering of end of text tables, figures and listings.

Comment [A2]: Mixed terminology use in International Council for Harmonisation (ICH) documents, e.g. study/trial, subject/patient, test drug/Investigational Product /investigational medicinal product, is standardised in CORE Reference, mostly to that used in the Clinical Data Interchange Standards Consortium (CDISC) Glossary. Applied Clinical Trials, December 2011: http://www.cdisc.org/system/files/all/standard_category/application/pdf/act1211_011_043_gr_glossary.pdf or an alternative authoritative source. **Study**, **subject** and **Investigational Product** are used in CORE Reference.

ICH E3 mixed use of 'applicant' and 'Sponsor' is standardised to 'Sponsor' because only a fraction of CSRs eventually end up in regulatory submission dossiers.

Note that substitution of the ICH E3 terms 'trial' and 'patient' with CORE Reference terms 'study' and 'subject', using unshaded CORE Reference text, are not further commented on.

Comment [A3]: ICH E3 uses 'test drug/ investigational product'. Clarification of terminology to 'Test Product'. See Preface for explanation of related terms.

Comment [A4]: Clarification as may not be available in some early phase studies.

Comment [A5]: Transparency is aided by inclusion of the registry name(s) (e.g. Clinicaltrials.gov, European Union Drug Regulating Authorities Clinical Trials [EudraCT] Database) and identifier(s) to allow linkage of the CSR to the registered protocol.

Comment [A6]: Data cut-off date(s) is important for pharmacovigilance. Transparency is aided by improved tracking of study data from the current study that might be included in other reports.

Title page continued:

- The name, qualifications and affiliation of Principal Investigator (PI) (for single-centre studies) or Coordinating Investigator (CI) (for multi-centre studies), or the Sponsor's Responsible Medical Officer (SRMO)

Comment [A7]: See Preface for concept and definitions of commercially confidential information (CCI [red comments in CORE Reference]) and protected personal data (PPD [blue comments in CORE Reference]) and how these relate to the 'secondary use CSR' for public disclosure.

Comment [A8]: Qualifications, e.g. MD, MBBS etc. assure that individuals are suitably qualified. This is an important requirement for the 'secondary use CSR' for public disclosure.

Comment [A9]: Clarification on how an investigator is designated PI or CI. This depends on whether the study is single- or multi-centre.

Comment [A10]: Consider for CCI and PPD impact:
Individual name(s) and affiliation(s) may be considered for CCI and PPD impact in the 'secondary use CSR' for public disclosure.

Note that the European Medicines Agency (EMA) does not consider PI/CI and Sponsor Signatory name as CCI and will not allow redaction in the 'secondary use CSR' (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 43 and page 50 of 91.

Note that the Sponsor's Responsible Medical Officer (SRMO) and the Sponsor Signatory may not always be the same individual. If the SRMO is an externally-contracted designee, the Sponsor may have their own employee as the Sponsor Signatory.

Title page continued:

- The name of company/Sponsor signatory (the person responsible for the clinical study report [CSR] within the company/Sponsor) should appear on this page; the name, telephone number and email of the company/Sponsor contact persons for questions arising during review of the CSR should be included in Appendix 16.1.4 and must be included in the letter of application if the CSR is included in a submission dossier

Comment [A11]: ICH E3 specifies 'fax number', but this is superseded by 'email'.

Comment [A12]: Consider for CCI and PPD impact: CSR text and CSR Appendices 16.1.1, 16.1.2 and 16.1.9 will be publicly disclosed (EMA Policy 0070 effective 1 Jan 2015: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf). and March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 88 of 91: 'To be noted that the same CCI, PPD and publication principles will apply to EU as well as non-EU studies in the context of Policy 0070'.

Suggest to include named individuals (other than the PI/CI and Sponsor Signatory in Appendix 16.1.4) to minimise redaction need in the 'secondary use CSR' for public disclosure.

Comment [A13]: ICH E3 gives the option to include contact information for the 'CSR contact' either on the CSR title page or in the 'letter of application'.
The 'letter' referred to is the Sponsor's letter to the regulatory authority (for CSRs included in a submission dossier).

Comment [A14]: Consider for PPD impact: Suggest to exclude 'CSR contact' from the CSR title page to minimise redaction need in the 'secondary use CSR' for public disclosure.

Comment [A15]: To ensure that the 'CSR contact' remains linked with the CSR, suggest inclusion of their details in Appendix 16.1.4.

Title page continued:

- Statement indicating whether the study was performed in compliance with International Council for Harmonisation (ICH) guideline on Good Clinical Practice (GCP), including the archiving of essential documents
- Version and date of the report: identify any earlier reports from the same study by title, version and date. Indicate that this is the 'primary use CSR' for regulatory submission.

An example Title Page follows:

Comment [A16]: Clarification that GCP is from International Council for Harmonisation (ICH). See: http://www.ich.org/about/organisational-changes.html which states that as of 23 Oct 2015, ICH is The International **Council for** Harmonisation (formerly the International **Conference on** Harmonisation).

Comment [A17]: Statement to the effect that the study was conducted according to the ethical principles that have their origin in the Declaration of Helsinki (DoH) is common. Add if appropriate. Note that Food and Drug Administration (FDA) do not support the DoH in its entirety.

Comment [A18]: Consider for CCI and PPD impact: Inclusion of report version (final version to regulatory authorities should always be 'approved'). Omission may result in precursor (draft) reports being submitted and, eventually might end in the incorrect report version being redacted and publicly posted.

Comment [A19]: Consider for CCI and PPD impact: For the 'secondary use CSR' for public disclosure, indicate that this is a redacted version CSR for public disclosure.
Additional insight note: March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) Chapter 2, Section 3.3 for a summary of the submission process for the entire Marketing Authorisation Application (MAA) for public disclosure (of which the 'secondary use CSR' is a component), in the EU. Applicants are required to submit 2 packages to EMA:
- 'Redaction Proposal Version' package
- 'Final Redacted Version' package.

Refer to the 'Redaction Proposal Version' process (page 14 of 91) and 'Final Redacted Version' process (page 26 of 91) packages and follow the requirements.

Brief process description: Complete the relevant template from the 'Redaction Proposal Version' package with a summary of CSR redacted information - one justification table is required per CSR (note this is a separate document to the CSR submitted with the 'Redaction Proposal Version' package and is not published). The 'Final Redacted Version' package includes the cover letter including "Confirmation that the clinical reports submitted for scientific evaluation are the same as that submitted for publication, in the Redaction Proposal and Final Redacted Versions, except for the redactions". PPD anonymisation methodology is included in a separate anonymisation report which is published.

See also 'Clinical data publication' page on EMA website:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa
and EMA news and events page:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid
This additional insight note may be disregarded for CSRs intended for submission in regions outside the EU.

Example Title Page

CLINICAL STUDY REPORT:
FULL VERSION FOR REGULATORY SUBMISSION/
REDACTED VERSION FOR PUBLIC DISCLOSURE

STUDY TITLE

Test Product: *Drug name*

(If not apparent from title, include brief description of development phase, indication studied, study design and type, duration, dose, and subject population.)

Sponsor's Responsible Medical Officer name and qualifications
Sponsor name
Sponsor address
or
Principal or Coordinating Investigator name and qualifications
Principal or Coordinating Investigator affiliation

Sponsor's Signatory name

Protocol Number: **[Trial Registry] Number(s):**

Study Initiation Date: *dd-Mmm-yyyy* (**Early Termination Date:** *dd-Mmm-yyyy*)
(Data Cut-off Date: *dd-Mmm-yyyy*) (**Product Termination Date:** *dd-Mmm-yyyy*)

Study Completion Date: *dd-Mmm-yyyy*

Study Phase:

This study was/was not conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

Report Version and Date
(*Earlier reports from the same study by version and date*)

<*Confidentiality Statement*>

Comment [A20]: Can be prefixed with 'abbreviated' if the CSR is abbreviated.

Comment [A21]: Delete as applicable to the document version.

Note that CORE Reference makes content suggestions for the 'primary use CSR'. Comments within CORE Reference indicate individual CSR text portions that may potentially impact the 'secondary use CSR', which will be publicly disclosed, and should therefore be considered for modification or redaction in the 'secondary use CSR'.

Comment [A22]: Consider for PPD and CCI impact: Individual name and qualification will not be redacted in the 'secondary use CSR' for public disclosure. The address may be redacted if it is not an address of the Sponsor.

Comment [A23]: Consider for PPD and CCI impact:
Individual name(s) and affiliation(s) may be considered for CCI impact in the 'secondary use CSR' for public disclosure.
Note that EMA does not consider PI/CI name and address as CCI and will not allow redaction in the 'secondary use CSR' (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 50 of 91.

Comment [A24]: If not the SRMO.

Comment [A25]: Consider for PPD and CCI impact: Individual name may require redaction in the 'secondary use CSR' for public disclosure. Note that EMA does not consider Sponsor signatory name as PPD or CCI and will not allow redaction in the 'secondary use CSR'. See March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 43 of 91.

Comment [A26]: Delete as applicable. Regulatory authority quality assurance (QA) auditors are known to question how the claim of study conduct in compliance with GCP is supported.

Comment [A27]: Consider for CCI and PPD impact: Confidentiality statement may be added for 'primary use CSR' for regulatory submission, but not for redacted 'secondary use CSR'.

2. SYNOPSIS

<Deliberate wider line spacing below to allow optimal presentation of ICH E3 2012 Q&A text>

A brief *stand-alone synopsis without cross-reference to other sections of the CSR* or other documents (usually limited to three pages, *although longer is acceptable for more complex studies*) that summarises the study should be provided. *In addition to a brief description of the study design and critical methodological information* (what was actually done), *the synopsis should provide* a summary of all relevant results (e.g. if there are multiple endpoints, consider limiting to primary and secondary) obtained during the study, *as well as other critical information, including data on the study population, disposition of subjects, important protocol deviations and treatment compliance.* The synopsis should include numerical data to illustrate results, not just text or p-values (consider presenting results as summary tables to reduce the amount of text in the synopsis). The conclusions should exactly match the overall conclusions in the body of the report. *The use of a tabular format synopsis is not mandatory*.

An example Synopsis follows:

Comment [A28]: Per ICH E3 2012 Quesitons & Answers (Q & A) Point 2 for CSR synopsis: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf which updated this ICH E3 instructional text to state '*Since the synopsis will be used as a stand-alone document within a Common Technical Document, it should be written so that it can be understood and interpreted on its own, i.e. without the other sections of a CSR*'. Clarification is added to this effect, and to remind that 'other' documents should not be referenced either.

Comment [A29]: Per ICH E3 2012 Q & A Point 2 which updated ICH E3 instructional text to state the synopsis can be longer than 3 pages if it needs to be.
Awareness comment pending finalisation of ICH guidance: An example of '10 pages' (see also [updated since 2012 Q & A] ICH M4E_R2: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2__Step_2.pdf) is described as acceptable for more complex studies, with the proviso that 10 pages is not an absolute requirement or limit, but should not need to be exceeded considerably.

Comment [A30]: Per ICH E3 2012 Q & A Point 2: '…*the synopsis should provide efficacy and safety results, as well as*…' To ensure no relevant results are omitted inadvertently, this requirement is captured by 'all relevant results'.

Comment [A31]: Per ICH E3 Q & A Point 2.

Comment [A32]: Suggestion to add clarity to presentation format.

Comment [A33]: Annex 1 referenced in ICH E3 and described as 'an example of a synopsis format used in Europe' is placed *in situ* in CORE Reference to ensure all relevant information is captured. The example Synopsis below includes all ICH E3 items and further enhancements with rationales for their inclusion.

Comment [A34]: For EU studies, also see: http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm.
Additional items are required by the Clinical Trials Regulation (CTR) EU No. 536-2014: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf Annex IV Section A page L 158/69 – 'content of the summary of the results of the clinical trial'. Relevant additional items are suggested for inclusion in the example CSR synopsis below to facilitate dual use for posting via the EU portal. These items are indicated with explanatory comments and may be omitted for non-EU studies, or if the CSR synopsis is not intended for dual use.

Such items are marked in the Example Synopsis below as
'…required by CTR EU 536-2014. Omit for non-EU studies, or if no direct posting of synopsis'.

Example Synopsis

Name of Sponsor/Company (and Scientific and Public Contact Points, if applicable):

Name of Finished Product: [may vary across regions]

Name of Active Ingredient:

TITLE OF STUDY (protocol number; trial registry name and number; paediatric investigation plan (PIP) number if applicable):

PRINCIPAL/COORDINATING INVESTIGATOR NAME, NUMBER OF STUDY CENTRE(S) AND COUNTRIES: [Only count study centre(s) that entered subjects. Do not include individual centre Investigator names or addresses.]

PUBLICATION (REFERENCES) (if any): [Any publications – including abstracts or posters – of the study, as well as publications describing interim or *post-hoc* analyses]

STUDY PERIOD (defined as appropriate for study design): [Use same dates as on title page]

REPORTING PERIOD (include the date of the first and the last data collection included in this report. Include information about intermediate data analysis date, interim or final analysis stage, date of global end of the study):

PHASE OF DEVELOPMENT:

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ICH E3 text | *ICH E3 2012 Q&A text* | CORE Reference text | [Right margin comment=RATIONALE]

Comment [A35]: Present what was actually done, not what was planned to be done.

Comment [A36]: Page & volume number omitted from header box as submissions are made (in many regions) in electronic common technical document (eCTD) format. In regions where paper format is still used, page and volume numbers may be added.

Comment [A37]: **Scientific and public contact points are required by CTR EU 536-2014**. Omit for non-EU studies, or if no direct synopsis posting.

Consider for PPD impact: Redaction of names and contact details may be required in the 'secondary use CSR' for public disclosure.

Comment [A38]: **Required by CTR EU 536-2014**. Suggest to include protocol number, trial registry name and number universally.

Comment [A39]: Indication if study is part of a paediatric investigation plan (PIP) is **required by CTR EU 536-2014**. Omit for non-EU studies, or if no direct synopsis posting.

Comment [A40]: Consider for PPD and CCI impact:
Individual name may be considered for CCI impact in the 'secondary use CSR' for public disclosure.

Note that EMA does not consider PI/CI name as CCI and will not allow redaction in the 'secondary use CSR'(http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 50 of 91.

Comment [A41]: To support transparency.

Comment [A42]: The ICH E3 specifications: '(date of first enrolment)' and '(date of last completed)' may not always be appropriate to describe study period. Hence flexibility is suggested to allow the study period to be defined as appropriate to the individual study.

Comment [A43]: Inclusion of reporting period suggested to support long duration trials with one or more interim results analysis stage(s).

Comment [A44]: **Required by CTR EU 536-2014**. Suggest to include reporting period universally.

BACKGROUND AND RATIONALE FOR THE STUDY: [in brief, e.g. 1 paragraph, including any limitations: sources of potential bias and imprecisions and caveats; include measures of protection of subjects; include standard of care therapy]
OBJECTIVES:
METHODOLOGY: ***[brief description of the study design and critical methodological information]***
NUMBER OF SUBJECTS (planned and analysed): [population of subjects (including actual number of subjects included in the clinical trial in the Member State concerned, in the Union and in third countries); age group breakdown, gender breakdown]
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION (Summarise only – do not list all inclusion/exclusion criteria):
TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S):
DURATION OF TREATMENT:
CONTROL PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S):
<Deliberate empty cell to allow comments on right hand side of this page to be shown in full>

Comment [A45]: Background and rationale information, and all example elements are **required by CTR EU 536-2014**. Suggest to include all such information universally.

Comment [A46]: Suggested length for new section is 1 paragraph to limit overall synopsis length.

Comment [A47]: **Required by CTR EU 536-2014**. Omit for non-EU studies, or if no direct synopsis posting. Regulation uses 'Background therapy' (not a CDISC term and not widely understood) which is substituted with 'standard of care therapy' based on this definition from page L/158/7 (54) of the Regulation: '… auxiliary medicinal products (medicinal products used in the context of a clinical trial but not as investigational medicinal products), such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial'.

Comment [A48]: Number of subjects analysed may be considered part of the results. Present in Results 'Subject Disposition' if not here.

Comment [A49]: **Required by CTR EU 536-2014**. Omit for non-EU studies, or if no direct synopsis posting.

Comment [A50]: Suggest to mention important exclusion criteria if they help define the population better than only the summarised inclusion criteria. Delete 'AND EXCLUSION' as appropriate.

Comment [A51]: The ICH E3 term 'reference therapy' is standardised throughout CORE Reference to 'Control Product'. See Preface for explanation of terms related to Investigational Product.

1

ENDPOINTS:
Efficacy (if applicable):

Pharmacokinetics (if applicable):

Pharmacodynamics (if applicable):

Safety (include those measures taken to protect subjects):

Other endpoints (if applicable – may include quality of life, pharmacoeconomics, pharmacogenomics etc.):

STATISTICAL METHODS: [in brief, e.g. state the statistical analysis method used to analyse each primary and secondary endpoint. Details of covariates, adjustments for multiplicity etc. are not required. State if interim analyses were conducted.]

SUMMARY OF RESULTS AND CONCLUSIONS: [May include summary tables. All objectives and endpoints stated in the methodology part of the synopsis must be addressed in the results part of the synopsis. If an endpoint was not analysed, or results were not available at the time of the report, this should be stated. *Post-hoc* results and conclusions may be included, but must be clearly identified as being *post-hoc* with appropriate rationale.]

***Subject Disposition*: [brief summary only (to include number of subjects analysed if not included above, *data on the study population and treatment compliance*), and a 1-2 line *summary of any important protocol deviations* that affected the study.]**

Demography and Baseline Characteristics: [brief summary only.]

Efficacy Results: [Must include primary efficacy result. May include summary of other efficacy results.]

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Comment [A52]: In ICH E3 there is no requirement to present endpoints in the synopsis. Suggest endpoints should be presented with clear linkage to the underlying objective – example sub-headings are given.

Inclusion of endpoints section renders ICH E3 'Criteria for evaluation' (omitted) redundant with no loss of information.

Comment [A53]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf states '(mid page 2) "In defining an appropriate 'estimand' for each primary and secondary endpoint, and in determining a strategy for statistical analysis to derive estimated effects…"

The definition of 'estimand' is on slide 8 of the 2015 ICH Presentation: https://www.efspi.org/Documents/Leaders%20Meetings/6th/8.%20Chrissie%20Fletcher%20EFSPI%20Statistics%20Leaders%202015%20estimands.pdf

Estimands are expected to be considered at the study design stage, may be described in the protocol, and should be included in this section of the Synopsis, if available. See comment in Section 9.5 (Efficacy and Safety Variables), Terminology Table for further detail on estimand.

Comment [A54]: Suggestion to present results in table format to reduce the amount of text and add presentational clarity.

Comment [A55]: Alternative placement of 'subjects analysed' if not included in 'Number of Subjects (planned and analysed)' above.

Comment [A56]: Suggest that if important protocol deviations did affect the study, a brief explanation of the impact on results and conclusions only should be added.

Comment [A57]: The results structuring should reflect that of the endpoints presented in the Synopsis methods.

1

Pharmacokinetic Results (if applicable):

Pharmacodynamic Results (if applicable):

Safety Results:

Other Results (if applicable): [May include quality of life, pharmacoeconomics, pharmacogenomics, *post-hoc* results etc. If *post-hoc* results are included, they must be clearly identified as being *post-hoc*.]

***Post-hoc* Results (if applicable and if not integrated into Efficacy Results or included under 'Other Results'): [Any *post-hoc* results must be clearly indicated as being *post-hoc*.]**

Conclusions: [see Section 13.2 (Conclusions). For clinical studies replicating studies on already authorised Investigational Products and used in accordance with the terms of the marketing authorisation, summarise identified concerns in the overall results of the clinical study relating to relevant aspects of the efficacy of the Investigational Product. Any *post-hoc* conclusions must be clearly identified as being *post-hoc*.]

DATE AND VERSION OF THIS REPORT: [Include any earlier final reports from the same study by date, as applicable.]

1

Comment [A58]: *Post-hoc* results may be integrated with Other Results or may be presented separately. Further discussion around this topic is given in Section 11.1 of CORE Reference. Regardless of where *post-hoc* data is presented in the Synopsis, it must be clearly identified as being *post-hoc*.

Comment [A59]: Suggest that the conclusions here match those in, for example, Section 13.2.

Comment [A60]: **Required by CTR EU 536-2014**. Omit for non-EU studies, or if no direct synopsis posting.
Summary text for identified concerns should be in brief in the Synopsis, and can be supported with a more complete presentation in, for example, Section 13.

Comment [A61]: Suggest that date and version information should appear on all pages of the CSR, in addition to here.
Consider for CCI and PPD impact: This is also an extra safeguard to ensure the appropriate CSR version is publicly posted.

3. TABLE OF CONTENTS

The automatic table of contents should include:

- The page number or other locating information of each CSR text section, including tables and figures embedded in the text (in-text tables and figures)
- A list and the locations within the CSR of appendices, tabulations and any case report forms (CRFs) provided.

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Comment [A63]: ICH E3 requires '…a list and the locations within the study report of appendices, tabulations and any case report forms provided'.

The CSR text comprises a Synopsis and the main body text. The tables, figures, listings (TFLs) and appendices including selected CRFs - are often held separately in electronic folders at the time the CSR is finalised. Many years may elapse between finalisation of a CSR and subsequent inclusion of CSR text and appendices in a submission dossier.

The page locations of appendices, TFLs and CRFs may therefore be better defined later in the process. The CSR table of contents (ToC) may therefore only list these items without a page by page specification of their locations at the 'final CSR' stage of the documentary process.

Comment [A64]: Searchable datasets may be submitted in some regions (e.g. US), removing the need for content in Appendix 16.4. Appendix 16.4 may still be used in other regions, so this appendix is left *in situ*.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

A list of the abbreviations, and lists and definitions of specialised or unusual terms or unusual measurements units used more than once in the synopsis and more than once in the main CSR should be provided. On first mention (in both the synopsis and again in the main CSR text), abbreviated terms should be spelled out and the abbreviation indicated in parentheses. Common abbreviations (e.g. UK, USA) need not be defined. In the case where an abbreviation is the same for two different terms, e.g. American Diabetes Association (ADA) and Antidiabetic Agents (ADAs), one of the two terms should be written out in full in all instances to avoid any confusion.

Example:

ABBREVIATIONS

AE	Adverse event

DEFINITIONS OF TERMS

QT interval	The portion of an electrocardiogram between the onset of the Q wave and the end of the T wave.

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE AND/OR INSTITUTIONAL REVIEW BOARD

It should be confirmed that the protocol and any of its amendments, as well as information provided to subjects and any recruitment advertisements etc. were reviewed by an Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB), or any other Ethics Committee (EC). A list of all IECs, IRBs, or ECs consulted should be given in Appendix 16.1.3 and, if required by the regulatory authority, the name of the committee Chair should be provided.

5.2 ETHICAL CONDUCT OF THE STUDY

It should be confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (version as specified in the study protocol or if not specified, include the version here) and in accordance with ICH GCP.

5.3 SUBJECT INFORMATION AND CONSENT

<Deliberate wider line spacing below to allow optimal presentation of ICH E3 2012 Q&A text>

How and when informed consent was obtained in relation to subject enrolment (e.g. at allocation, pre-screening) should be described. Representative written information for the subject (patient information sheet [PIS]) and a sample informed consent form (ICF), designated as the master versions, *must be provided in the trial master file (TMF)*.

Comment [A65]: ICH E3 term 'report' is substituted with 'main CSR' to differentiate the main (body of the) report from the synopsis.

Comment [A66]: Clarification of ICH E3 text 'at first appearance in the text'. This supports 'stand alone' use of the Synopsis.

Comment [A67]: In the 'secondary use CSR' for public disclosure, such terms would even not require definition.

Comment [A68]: A list of abbreviations used in CORE Reference can be found on the last two pages of this document.

Comment [A69]: ICH E3 uses 'study'. This is clarified as 'protocol'.

Comment [A70]: Clarification that information provided to subjects is also reviewed by IEC/IRB.

Comment [A71]: The study may have used IECs and/or IRBs: IECs are generally used in Europe and IRBs are generally used in the US. For studies conducted outside Europe and the US, it may be that neither an IEC nor an IRB is used and instead an Ethics Committee (EC) reviewed the information. There is no need to specify which type of committee was used.

Comment [A72]: The FDA does not acknowledge some versions of the Declaration of Helsinki, hence the suggestion to mention which version was used (if not already specified in the protocol).

Comment [A73]: Reference to ICH GCP is included. However, Regulatory authority QA auditors are known to question how the claim of study conduct in compliance with GCP is supported, so suggest not to make this claim if the Sponsor is unable to support it.

Comment [A74]: Substitution of 'patient' with 'subject' in this title and consistently throughout because CORE Reference uses 'subject'. Use of either patient or subject in individual CSRs will be study-specific.

Comment [A75]: Omitted ICH E3 text 'if any'. There will always be patient information provided for all studies in the form of a PIS.

Comment [A76]: Deliberate use of the term PIS with no change from 'patient' to 'subject' as PIS is a widely used industry term.

Comment [A77]: Clarification that the master versions (and not the locally adapted versions) must be provided in the TMF (inclusion is no longer mandatory in Appendix 16.1.3 per ICH E3 2012 Q & A).

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The administrative structure of the study (e.g. Principal Investigator, Coordinating Investigator(s), steering committee, administration, monitoring and evaluation committees, institutions, statistician, central laboratory facilities, contract research organisation [CRO], clinical study supply management) should be described briefly in the body of the report, without mention of individual names or contact details (with some exceptions such as the name of the PI [for single-centre studies] or CI [for multi-centre studies]). Indicate the location of the trial master file (TMF).

In Appendix 16.1.4, provide a list of the investigators, abbreviated for studies with many centres to only the PIs of each centre, and a list of other persons whose participation materially affected the conduct of the study, each with general statements of qualifications for persons carrying out particular roles in the study, with only the name, degree, institutional affiliation and roles in the study. The listing should include:

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Comment [A78]: Consider for PPD impact:
In the EU, See March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) Chapter 3, Section 6 (Redaction of personal data of investigators, sponsor staff and applicant/marketing authorisation holder [MAH] staff) states: 'Personal data of individuals other than patients, i.e. investigators, sponsor staff and applicant/MAH staff will not be published with the following exceptions: The sponsor and CI signatories of the CSR and the identities of the investigator(s) who conducted the trial and their sites. However, their contact details and signature should be redacted. Personal data relating to all other clinical study personnel should also be redacted. Data pertaining to the above exceptions in other parts of the CSR will be redacted as they may give away geographical information (e.g. site number, site address, investigator names) that could be linked to patients and hence may enable their identification'.

The 'take-home message' is that only the names of the PI, CI and Sponsor signatory should be disclosed in the 'secondary use CSR' for public disclosure.

Comment [A79]: Consider for PPD and CCI impact:
Individual name(s) and affiliation(s) may be considered for CCI impact in the 'secondary use CSR' for public disclosure.

Note that EMA does not consider PI/CI name and address as CCI and will not allow redaction in the 'secondary use CSR' (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 50 of 91.

Comment [A80]: Per EMA pre-authorisation procedural advice for users of the centralised procedure'. 31 Mar 2016 EMA/339324/2007: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf. This may be omitted for non-EU studies. Included here as useful globally.

Comment [A81]: Slight rewording of ICH E3 text with no loss of meaning.

Comment [A82]: Suggest to restrict Investigator list for studies with many investigators, in the spirit of ICH E3 Q & A. All investigator names and their curricula vitae (CVs) will in any case be in the TMF.

Comment [A83]: Amalgamation of Investigator and 'other person' requirements into a consolidated statement with improved readability.

Comment [A84]: The requirement for CVs in Appendix 16.1.4 has been removed as per the ICH E3 2012 Q & A which states that CVs can be included in the TMF only.

a) Principal Investigators

b) Any other person carrying out observations of primary or other major efficacy variables, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist or house staff physician. It is not necessary to include in this list a person with only an occasional role, e.g. an on-call physician who dealt with a possible adverse event (AE) or a temporary substitute for any of the above

c) The author(s) of the report, including the responsible biostatistician(s).

Where signatures of the principal signatory investigators (PI or CI) are required by regulatory authorities, these should be included in Appendix 16.1.5 (see Annex I for an example signature form). Where these are not required, the signature of the Sponsor's responsible medical officer should be provided in Appendix 16.1.5.

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Comment [A85]: For studies with many centres, the possible list of all Investigators will be extensive. All Investigator details will be in the TMF in any case, so in the spirit of the ICH E3 2012 Q & A, suggest there is no need to duplicate in the CSR.

Comment [A86]: Consider for PPD impact: In the EU, See March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf). Persons under b) and c) will be listed only in (non-disclosed) Appendix 16.1.4 so there is no impact in the 'secondary use CSR' for public disclosure.

Comment [A87]: ICH E3 Annex II is CORE Reference Annex I.

Comment [A88]: In the EU, expect that CI should be designated in the protocol, per note for guidance on Coordinating Investigator signature of CSRs CPMP/EWP/2747/00: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003656.pdf.

Example administrative structure for inclusion in the CSR text, with roles and responsibilities:

PRINCIPAL INVESTIGATOR (for single-centre studies): [Name and country in which the PI is based only; refer to Appendix 16.1.4 for details]

COORDINATING INVESTIGATOR (for multi-centre studies): [Name and country in which the CI is based only; refer to Appendix 16.1.4 for details – delete if not applicable]

DATA MONITORING AND EVALUATION COMMITTEE(S): [Mention if used and refer to protocol, and amendments, in Appendix 16.1.1 for details – delete if not applicable]

CLINICAL LABORATORIES: [Mention if a central laboratory was used and include institution name(s) and address(es) only; refer to Appendix 16.1.1/16.1.4/16.1.10 for details]

CONTRACT RESEARCH ORGANISATIONS (CROs): [Mention if used; link CROs to study activities and include report authoring and biostatistics; include institution name(s) and address(es) only; refer to Appendix 16.1.1/16.1.4 for details]

OTHER ORGANISATIONS: [Mention if used and include institution name(s) and address(es) only; and refer to Appendix 16.1.1/16.1.4 for details, as applicable].

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Comment [A89]: Consider for PPD and CCI impact:
Individual name may be considered for CCI impact in the 'secondary use CSR' for public disclosure.

Note that EMA does not consider PI/CI name and address as CCI and will not allow redaction in the 'secondary use CSR' (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 50 of 91.

Comment [A90]: In the EU, expect that CI should be designated in the protocol, per note for guidance on Coordinating Investigator signature of CSRs CPMP/EWP/2747/00: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003656.pdf.

Comment [A91]: Consider for PPD and CCI impact:
Individual name may be considered for CCI impact in the 'secondary use CSR' for public disclosure.

Note that EMA does not consider PI/CI name and address as CCI and will not allow redaction in the 'secondary use CSR' (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 50 of 91.

Comment [A92]: For EU studies only: EMA pre-authorisation procedural advice for users of the centralised procedure' 31 Mar 2016 EMA/339324/2007: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf
See 32. How are initial marketing authorisation applications (MAAs) validated at the EMA: 'How to avoid most common GCP validation issues'.
Information required in Appendix 16.1.4:

- **… clear description of study administrative structure (clear identification of Sponsor and parties who have performed the monitoring, data management, statistics, laboratory assessments, randomization, site(s) of manufacture, other applicable activities and the location of the TMF) preferably in a tabular form and indicating name and address of the site where each activity was performed, responsibilities and scope of each activity…identified in the CSR of each study, … in Section 6, or Appendix 16.1.4.**

Consider for PPD impact: CORE Reference suggests to include placement of detailed information above in Appendix 16.1.4 and not in the main CSR text.
Consider for CCI impact:
See March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf). Chapter 4, Section 3.2.3.1 (General or administrative information) states that the following will not be considered CCI by EMA: 'Names of all CROs and vendors involved in trial-related duties and functions (e.g. central laboratories, Interactive Voice Response System (IVRS) provider, image reading centres, conduct of assays)'. Partnerships not in the public domain are not exempt.

7. INTRODUCTION

The Introduction should contain a brief statement (1 to 3 pages) placing the study in the context of the development of the Investigational Product, relating the critical features of the study to that development. Include a brief statement on the drug being studied. Include the medical rationale for the development of the study (avoiding commercially confidential information [CCI] not specifically needed to explain the medical need) and including brief text on current treatments, i.e. available at the time of protocol design. Any guidelines that were followed in the development of the protocol or any other agreements/meetings between the Sponsor and regulatory authorities that are relevant to the particular study, should be identified or described. Especially for studies with multiple consecutive analyses and reports, the introduction should contain a clear statement on which cut-off date(s) is(are) used for the analyses reported (e.g. date of database release). If the study is terminated before its planned end, this should be noted and explained.

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Comment [A93]: ICH E3 gives a maximum of 1 page. Suggest a reasonable maximum is 3 pages, given the additional CORE Reference suggested information for inclusion.

Comment [A94]: ICH E3 text states 'test drug/investigational product' Terminology is standardised to 'Investigational Product' throughout CORE Reference. See Preface for explanation of 'Investigational product' terminology choices.

Comment [A95]: ICH E3 also lists: 'aims, target population, treatment, duration, primary endpoints'. All this information is included in the sections that follow and is repetitive, so it is suggested that this can be omitted from the Introduction.

Comment [A96]: Consider for CCI impact: Possible sensitive company information (i.e. CCI) could be revealed in the 'secondary use CSR' for public disclosure, so care taken to avoid this in the Introduction of the CSR for regulatory submission will remove the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A97]: Transparency is aided by explaining currently available treatments.

Comment [A98]: Any such agreements/meetings should also be cross-referred to in, for example, Section 9.5.1 (Efficacy and Safety Measurements Assessed and Schedule of Assessments), or to any other relevant section, as appropriate.

Comment [A99]: Cut-off dates and early termination dates, if applicable, are also recommended for placement in, for example, Section 9.6 Data Quality Assurance.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1 OBJECTIVES

A statement describing the overall purpose(s) of the study should be provided. The objectives should be per protocol (and any global amendments), with only minor adjustments for tense and grammar permitted.

8.2 ENDPOINTS

Endpoints should be per protocol (and include any global amendments), with only minor adjustments for tense and grammar permitted.

9. INVESTIGATIONAL PLAN

The investigational plan description must be based on the protocol and all of its amendments. It should reflect the situation after implementation of the last amendment. It is particularly important to clarify features that are not well described in the protocol or its amendments. Throughout, it should be made clear which key procedures or analyses had been planned in the original protocol and which had been introduced via subsequent protocol amendments.

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Comment [A100]: Brief, bullet-point objectives, divided into primary, secondary and exploratory objectives and with a primary, secondary and exploratory hierarchy to match those of endpoints and variables – are typically expected in the protocol.

The key CORE Reference message is that the CSR sections should match each other starting with the objectives which drive the endpoints, which in turn inform the content of, for example, Section 9.5.

Comment [A101]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf states '(mid page 2) "In defining an appropriate 'estimand' for each primary and secondary endpoint, and in determining a strategy for statistical analysis to derive estimated effects…"

The definition of 'estimand' is on slide 8 of the 2015 ICH Presentation: https://www.efspi.org/Documents/Leaders%20Meetings/6th/8.%20Chrissie%20Fletcher%20EFSPI%20Statistics%20Leaders%202015%20estimands.pdf Estimands are expected to be considered at the study design stage, may be described in the protocol, and should be included in this section, if available.
See comment in Section 9.5 (Efficacy and Safety Variables), Terminology Table for further detail on estimand.

Comment [A102]: In ICH E3 there is no requirement to present endpoints in the CSR. Suggest endpoints should be presented and clear linkage should be made to the underlying objective.

Comment [A103]: See, for example, Section 9.8 (Changes in the Conduct of the Study or Planned Analyses).

9.1 OVERALL STUDY DESIGN AND PLAN

The overall study plan and design (configuration) of the study (e.g. parallel, crossover) should be described briefly but clearly. Include a schematic of the study design (see Example Figure 9.1) in most cases, even if not provided in the protocol. The schematic should be presented early in the 'Overall study design and plan'. If other studies used a very similar protocol, it may be useful to note this and describe any important differences. The actual protocol and any changes should be included as Appendix 16.1.1 and a sample CRF (unique pages only; i.e. it is not necessary to include identical pages from forms for different evaluations or visits) as Appendix 16.1.2 - see (Section 16 Appendices). If any of the information in this section comes from sources other than the protocol, these should be identified.

Brief summary information should be provided (limited to one or two pages) as follows:

- Treatments studied (specific drugs, doses and procedures)
- Subject population studied and the number of subjects to be included in each treatment group and overall
- Level and method of blinding/masking (e.g. open, double-blind, single-blind, blinded evaluators and unblinded subjects and/or Investigators)
- Kind of control(s) (e.g. placebo, no treatment, active drug, dose-response, historical) and study configuration (parallel, crossover)
- Method of assignment to treatment (randomisation, stratification)
- Sequence and duration of all study periods, including pre-randomisation and post-treatment periods, treatment withdrawal periods and single- and double-blind treatment periods. When subjects are randomised should be specified. It is usually helpful to display the design with a schematic (see Example Figure 9.1)
- Any safety, data monitoring or special steering or evaluation committee(s)
- Any interim analyses, including data cut-off dates
- If the study is terminated (before its planned end), this should be noted.

An accounting of tests performed by visit is not required.

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Comment [A104]: Omitted unnecessary final word of ICH E3 section title '- description' as does not add anything.

Comment [A105]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf states 'A clear definition of an estimand is important … since the choice of estimand is linked to important considerations around trial design, conduct and analysis. These include, for example, duration of patient follow-up, adherence to randomised treatment, use of alternative medications after discontinuation of randomised treatment and methods to handle missing data in the statistical analysis.'
Such design aspects are expected to be considered at the study design stage, may be described in the protocol, and should be considered for inclusion in this section, if available.

Comment [A106]: Substitution of ICH E3 text 'using charts and diagrams as needed' to add clarity.

Comment [A107]: It may be difficult to reference other study designs as not all may be accessible to the same parties.

Comment [A108]: Substituted ICH E3 text 'case report form (CRF)' with 'CRF' due to first use of this abbreviation earlier in CORE Reference.

Comment [A109]: Suggest that the content of this section should be a brief summary as all topics are covered in more detail in later sections.

Comment [A110]: See, for example, Section 9.4 (Treatment).

Comment [A111]: ICH E3 states 'graphically with a flow chart which includes timing of assessments (see [ICH E3] Annexes IIIa and IIIb for an example)'.
ICH E3 Annexes IIIa and IIIb are redesigned and amalgamated to create Example Figure 9.1 entitled 'Schematic of Study Design for Protocol xxx'. Placement of this figure early on in this section is intended to show study design clearly by schematic. The second part of Annex IIIa is unnecessary since that is just a repeat of the table of assessments, so this is omitted altogether. The table of assessments (Table 9.1) is provided in Section 9.5.1.

Comment [A112]: Suggest dates are included to aid transparency and add clarity.

Comment [A113]: Suggest that a list of tests by visit is not required. It is typically already listed in the protocol.

Example Figure 9.1. Schematic of Study Design for Protocol xxx

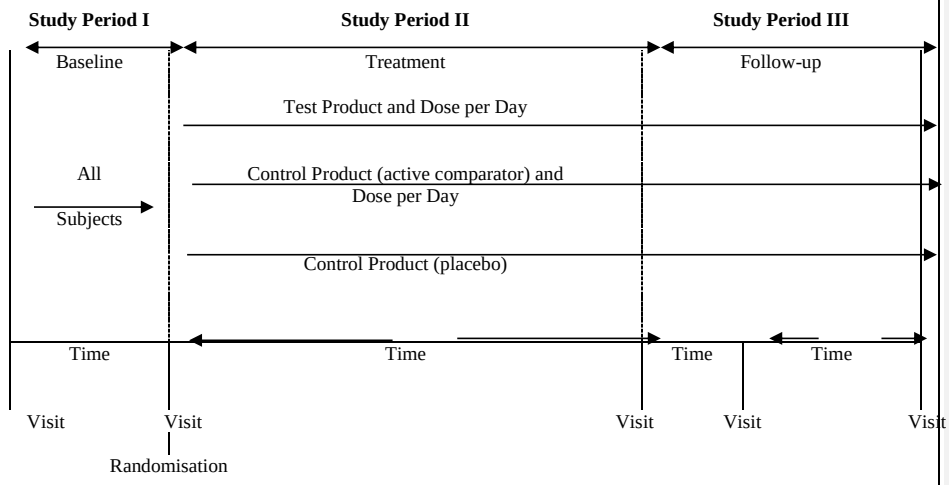

Figure footnote, if needed

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The specific control chosen and the study design used should be discussed, as necessary, including details of statistical support for those choices. Examples of design issues meriting discussion follow.

Generally, the control (comparison) groups that are recognised are placebo concurrent control, no treatment concurrent control, or active comparator concurrent control, dose comparison concurrent control, and historical control. The rationale for the choice of Control Product should be provided (e.g. if the Control Product was placebo, explain why an active comparator was not used). If an active comparator was used, state whether the dose was the standard recommended dose. If not, it is important to explain why. For a historically controlled study, it is important to explain how the particular control was selected, what other historical experiences were examined, if any, and how their results compared to the control used. In addition to the type of control, other critical design features that may need discussion are use of a crossover design and selection of subjects with particular prior history, such as response or non-response to a specific drug or member of a drug class. If randomisation was not used, it is important to explain how other techniques, if any, guarded against systematic selection bias.

Comment [A114]: Suggest to include protocol number in figure title to aid regulatory reviewers who often copy and paste key CSR information into their own summary documents.

Similarly, this is suggested for all in-text tables and figures (see later in CORE Reference).

Comment [A115]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf

Estimands are expected to be considered at the study design stage, may be described in the protocol, and relevant text could be placed in this section, if not in Section 8, and if available.

Note that Health Canada, refer specifically to the E9 Addendum, and advise that the estimand, how it was derived/decided and rationales/reasoning behind it, need to be explained well in the CSR.

Comment [A116]: Suggest to include brief early phase summary data to support later phase study design if it is helpful for study design justification.

Comment [A117]: ICH E3 uses 'active treatment' which is replaced with 'active comparator' throughout CORE Reference. See Preface for explanation of 'Investigational product' terminology choices.

Comment [A118]: ICH E3 text (single sentence) relocated here from Section 9.4.3 Method of assigning patients to treatment groups.

Known or potential problems associated with the study design or control group chosen should be discussed in light of the specific disease and therapies being studied. For a crossover design, for example, there should be consideration, among other things, of the likelihood of spontaneous change in the disease and of carry-over effects of treatment during the study.

If efficacy was to be demonstrated by showing equivalence, i.e. the absence of a specified degree of inferiority of the new treatment compared to an established treatment, problems associated with such study designs should be addressed. Specifically, a basis for considering the study capable of distinguishing active from inactive treatment should be provided. Support may be provided by an analysis of previous studies similar to the present study with respect to important design characteristics (subject selection, study endpoints, duration, dose of active comparator, concomitant therapy, etc.) showing a consistent ability to demonstrate superiority of the active comparator to placebo. How to assess the ability of the present study to distinguish effective from ineffective therapy should also be discussed. For example, it may be possible to identify a treatment response (based on past studies) that would clearly distinguish between the treated population and an untreated group. Such a response could be the change of a measure from baseline or some other specified outcome like healing rate or survival rate. Attainment of such a response would support the expectation that the study could have distinguished the active drug from an inactive drug. There should also be a discussion of the degree of inferiority of the therapy (often referred to as the delta value), namely that the degree of inferiority of the therapy that the study was intended to show was not exceeded. If Number Needed To Treat has been used to measure treatment effect in preference to measures such as relative risk or odds ratio then justification for that decision should be included.

The limitations of historical controls are well known (difficulty of assuring comparability of treated groups, inability to blind Investigators to treatment, change in therapy/disease, difference due to placebo effect, etc.) and deserve particular attention.

Other specific features of the design may also deserve discussion, including an adaptive study design, presence or absence of washout periods and the duration of the treatment period, especially for a chronic illness.

The rationale for dose and the basis for selecting each subject's dose or dose ranges should be explained, if it is not obvious (e.g. Test Product animal data, prior experience with Test Product in humans). The procedures for selecting each subject's dose or dose ranges of Test Product or active comparator should be described. These procedures can vary from simple random assignment to a selected fixed drug/dose regimen, to some specified titration procedure, to more elaborate response-determined selection procedures, e.g. where dose is titrated upward at intervals until intolerance or some specified endpoint is achieved. Procedures for back-titration, if any, should also be described. The procedures used to seek evidence of "escape" from drug effect at the end of the dose-interval, such as measurements of effect just prior to dosing, should be described. Similarly, in a parallel design dose-response study, the choice of doses should be explained.

Comment [A119]: Slight rewording of ICH E3 sentence with no loss of meaning.

Comment [A120]: Clarification of the ICH E3 text 'active control' as 'active comparator' here and below.

Comment [A121]: Clarification of ICH E3 text by addition of a clause.

Comment [A122]: Clarification on how to justify Number Needed To Treat, if used.

Comment [A123]: Included to reflect evolving drug development landscape.

Comment [A124]: Clarification to encourage inclusion of detail on how doses in the study were selected, and dose for each subject together with the reasons for selecting the timing for the dose. This is relocated text from the ICH E3 Sections 9.4.4 (Selection of Doses in the Study) and 9.4.5 (Selection and Timing of Dose for Each Subject). Only the actual dose and its timing in relation to meals etc is now coved in the 'Treatment' Section 9.4.

Comment [A125]: Parenthetic examples opposite are intended to generalise the ICH E3 text 'For example, once daily dosing with a short half-life drug whose effect is closely related in time to blood level is not usually effective; if the study design uses such dosing, this should be explained, e.g., by pointing to pharmacodynamic evidence that effect is prolonged compared to blood levels' which is omitted. Note that ICH E3 text on dose and dose ranges relocated here from ICH E3 Section 9.4.4, is a combination of the ICH E3 Section 9.4.4 text and the similar (less detailed) text from ICH E3 Section 9.2.

Comment [A126]: ICH E3 terminology 'test drug/investigational product and active control/comparator' is substituted with CORE Reference terminology.

Comment [A127]: ICH E3 text starting 'The procedures…' to end of paragraph is relocated from ICH E3 Section 9.4.5.

The choice of any non-Investigational Product therapy should be justified, and the therapeutic regimen described.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

The subject population and the selection criteria used to enter the subjects into the study should be described. The inclusion criteria should be taken from the protocol, including any numbering, with only minor adjustments for tense and grammar permitted.

Screening criteria and any additional criteria for randomisation or entry into the Investigational Product treatment part of the study should be described. If there is reason to believe that there were additional entry criteria not defined in the protocol, the implications of these should be discussed. For example, some Investigators may have excluded, or entered into other studies, subjects who were particularly ill or who had particular baseline characteristics.

9.3.2 Exclusion Criteria

The criteria for exclusion at entry into the study should be specified and the rationale (e.g. safety concerns, administrative reasons or lack of suitability for the study) provided. The exclusion criteria should be taken from the protocol. The impact of exclusions on the generalisability of the study should be included in the discussion (see for example, Section 13 Discussion and Overall Conclusions).

9.3.3 Removal of Subjects from Therapy or Assessment

The predetermined reasons for removing subjects from therapy or assessment observation, if any, should be described, as per protocol, as should the nature and duration of any planned follow-up observations in those subjects. In some studies (e.g. cancer studies) subjects can be withdrawn from treatment (e.g. due to disease progression) but they remain in the study so they can be followed for long-term outcome. In such cases particularly, and in all studies generally, a clear distinction should be made between discontinuations (i.e. stop treatment), where the subject remains in the study and completes some or all of the protocol-defined procedures, and withdrawals (i.e. stop treatment and stop all protocol-defined procedures) from the study, where no further information is collected on the subject.

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Comment [A128]: Clarification to encourage that the choice and regimen of 'non Investigational Product therapy' is described.
See Annex 1 of European Commission guidance on IMPs and NIMPs, 18 March 2011: http://ec.europa.eu/health/files/eudralex/vol-10/imp_03-2011.pdf for examples of non-IPs.
These are summarised and clarified as:
- Protocol required underlying therapy
  - Standard of care therapy (protocol required to treat the indication)
  - Concomitant therapy (protocol required for a condition which is not the indication for which the IP is being tested)
- Rescue medication
- Challenge agent
- Medicinal product used to assess endpoints (e.g. Positron emission tomography [PET] ligand).

Comment [A129]: The following ICH E3 text has been omitted '…and the suitability of the population for the purposes of the study should be discussed'.
In practice, this is often addressed in submission summary documents and is misplaced here.

Comment [A130]: The following ICH E3 text has been omitted 'Specific diagnostic criteria used, as well as specific disease requirements (e.g. disease of a particular severity or duration, results of a particular test or rating scale(s) or physical examination, particular features of clinical history, such as failure or success on prior therapy, or other potential prognostic factors and any age, sex or ethnic factors) should be presented' - as this level of detail should be addressed within the protocol.

Comment [A131]: ICH E3 text 'test/drug/investigational product' is substituted with CORE Reference term 'Investigational Product'.

Comment [A132]: The protocol may or may not group the exclusion criteria as reporting requries –see the ICH E3 parenthetic text. Grouping should be considered at reporting.

Comment [A133]: The ICH E3 reference to discussing impact of exclusions on generalisability in an overview of safety and efficacy is omitted as this is considered to be misplaced. The 'impact of exclusions' sentence is replicated in Section 13 to avoid inadvertent omission.
ICH E3 phraseology '…should be included in Section 13 of the study report' is reworded (to remove misplaced inference of ICH E3 being a template) as '…should be included in the discussion'. The reworded text is shaded as ICH E3 text because the meaning is not different.

Comment [A134]: Further clarification is provided on differences between removal from treatment and removal from the study.

Comment [A135]: Post-withdrawal contact with a subject may be protocol-defined.

9.3.4 Stopping or Suspending the Study

Protocol-defined circumstances under which the study would be stopped or suspended should be taken from the protocol with only minor adjustments for tense and grammar permitted.

9.4 TREATMENT

9.4.1 Treatments Administered

The precise treatments or diagnostic agents to be administered in each arm of the study, and for each period of the study, should be described, as per protocol, including route and mode of administration, dose and dosage schedule.

Where the Investigational Product is an add-on treatment to the current standard of care (which may be variable) then the standard of care should be described within the "Treatments Administered" section, but should be clearly distinguished from Investigational Product. These and other non-Investigational Product treatments (such as concomitant therapy, rescue medication, challenge agents etc.) administered should also be described and be clearly distinguished from Investigational Product.

Example subheadings may include:

9.4.1.1 Investigational Product(s)
9.4.1.2 Non-Investigational Product(s)

Treatment options available to subjects post-study (either on completion of study, or after premature withdrawal/termination) should be described.

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Comment [A136]: If the study is terminated before its planned end, this should be reflected, for example, in Section 7 (Introduction) and Section 9.1 (Overall Study Design and Plan).

Comment [A137]: Clarification to encourage inclusion of study termination criteria which are not mentioned in ICH E3, but are expected to be included in the protocol.

Comment [A138]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf states 'A clear definition of an estimand is important …since the choice of estimand is linked to important considerations around trial design, conduct and analysis. These include, for example, duration of patient follow-up, adherence to randomised treatment, use of alternative medications after discontinuation of randomised treatment and methods to handle missing data in the statistical analysis.'
Such design aspects are expected to be considered at the study design stage, may be described in the protocol, and should be considered for inclusion in this section if relevant to individual study design and if available.

Comment [A139]: See Annex 1 of European Commission guidance on IMPs and NIMPs, 18 March 2011: http://ec.europa.eu/health/files/eudralex/vol-10/imp_03-2011.pdf for examples of non-Investigational Products. These are summarised and clarified as:

- Protocol required underlying therapy
  - Standard of care therapy (protocol required to treat the indication);
  - Concomitant therapy (protocol required for a condition which is not the indication for which the IP is being tested).
- Rescue medication
- Challenge agent
- Medicinal product used to assess endpoints (e.g. PET ligand).

9.4.2 Identity of Investigational Product(s)

<Deliberate wider line spacing below to allow optimal presentation of ICH E3 2012 Q&A text>

In the text of the report, a brief description of the Investigational Product(s) (formulation, strength, batch number[s] ([*list only without per-subject linkage*]), source [company name and country of source]) should be given. If the batch number list is extensive, it may be placed in Appendix 16.1.6.

The source (company name and country of source) of placebos and active comparator(s) should be provided. Any modification of active comparator(s) from their usual commercial state should be noted and the steps taken to assure that their bioavailability was unaltered should be described.

For long-duration studies of Investigational Products with limited shelf-lives or incomplete stability data, the logistics of resupply of the materials should be described. Any use of Investigational Product, or any study supplies past their expiry date should be noted and subjects receiving them identified. If there were specific transportation and storage requirements, these should also be described.

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Comment [A140]: ICH E3 text 'test/drug(s)/investigational product(s)' is substituted with CORE Reference term 'Investigational Product(s)'.

Comment [A141]: Per ICH E3 2012 Q & A Point 3, replace per subject batch number listing in Appendix 16.1.6 with a simple list of Investigational Product batch numbers (without subject linkage). Although the parenthetic text does not appear verbatim in the ICH E3 2012 Q & A, it is shaded as ICH E3 2012 Q & A text because the text in ICH E3 2012 Q & A reads: '*Supportive documents, such as … batch numbers per subject are in the TMF or clinical supply database and should generally not be included in the CSR appendices*.'

Comment [A142]: As Investigational Product is defined as Test Product and Control Product (including active comparator and placebo), all such batch numbers should be listed (without per subject linkage).

Comment [A143]: Consider for CCI impact: Source information detail should be carefully considered with regard for CCI in the 'primary use CSR' for regulatory review to minimise piecemeal redaction in the 'secondary use CSR' for public disclosure.

For EU, see pre-authorisation procedural advice for users of the centralised procedure. July 2015 EMA/339324/2007. Section 38: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf.

Site of manufacture and site of release in Europe (of Investigational Product) is required.

This may be omitted for non-EU studies.

Comment [A144]: ICH E3 uses the wording 'active control/comparator product(s)' This is clarified as 'active comparator(s)' here and throughout.

Comment [A145]: ICH E3 term 'test materials' is further clarified.

Comment [A146]: Clarification added to ensure use of any out of date product is not overlooked.

9.4.3 Avoidance of Bias

9.4.3.1 Methods of Assigning Subjects to Treatment Groups

Typical methods for avoidance of selection bias include, but are not limited to, randomisation.

The specific methods used to generate random numbers, assign subjects to treatment groups, e.g. centralised allocation, allocation within sites, adaptive allocation (that is, assignment on the basis of earlier assignment or outcome) should be described, as per protocol. The protocol should also describe any stratification factors necessary and whether blocking procedures should be used. If necessary, any references should be cited. The process for implementing the randomisation schedule (e.g. interactive voice response system) should be specified. The CSR text should include the information given in the protocol along with any further information on the randomisation method available following study unblinding (e.g. use of mixed block sizes). Any unusual features of the randomisation method should be explained.

A table exhibiting each subject identifier, their randomisation code and treatment assigned should be presented in Appendix 16.1.7. For a multicentre study, the information should be given by centre. If stratification factors were used in the randomisation schedule, the table should include which level of each stratification factor(s) each subject was assigned to.

9.4.3.2 Blinding and Unblinding

A description of the specific procedures used to carry out blinding should be provided (e.g. how bottles were labelled, labels that reveal blind-breakage, sealed code list/envelopes, double-dummy techniques), including the circumstances in which the blind would be broken for an individual or for all subjects, e.g. for serious AEs (SAEs), the procedures used and who had access to subject codes. If the study allowed for some Investigators to remain unblinded (e.g. to allow them to adjust medication), the means of shielding other Investigators should be explained. Measures taken to ensure that Test Product and Control Product (which may include active comparator[s] and placebo) were indistinguishable and evidence that they were indistinguishable, should be described, as should the appearance, shape, smell, and taste of the test material. Measures to prevent unblinding by laboratory measurements, e.g. by centralised reading, if used, should be described.

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Comment [A147]: ICH E3 Section 9.4.3 (Method of Assigning Subjects to Treatment Groups) and ICH E3 Section 9.4.6 (Blinding) often overlap. Suggest merging the content of these two ICH E3 methodological sections and appropriately renaming to, for example, 'Avoidance of Bias'.

Comment [A148]: ICH E3 states 'The method of generating random numbers should be explained' later in this section. This is more appropriately incorporated earlier in the section to sit alongside the other methods, with minor text adjustment.

Comment [A149]: Clarification to indicated that the methods are expected to be described in and sourced from the protocol.

ICH E3 states 'A detailed description of the randomisation method, including how it was executed, should be given in Appendix 16.1.7'. This would be duplicative of the protocol text, is not considered necessary and is therefore omitted.

Comment [A150]: Further clarity is provided on the expected level of methodological detail for generating the randomisation schedule. See the text starting from 'The process for implementing…' to the end of this paragraph.

Comment [A151]: Slight modification of ICH E3 text with no loss of meaning.

Comment [A152]: The following ICH E3 text: 'For a historically controlled study, it is important to explain how the particular control was selected, what other historical experiences were examined, if any, and how their results compared to the control used' is integrated more appropriately with content in CORE Reference Section 9.2 Discussion of study design including choice of control groups.

Comment [A153]: Suggest procedures for unblinding should accompany the blinding procedures, hence title for this content is adapted appropriately.

Comment [A154]: ICH E3 text reads 'Measures taken to ensure that test drug/investigational product and placebo were indistinguishable…' This text is clarified in line with the Investigational Product definitions defined in the Preface.

If there was a data monitoring committee (DMC) and/or an adjudication or evaluation committee, either within or outside the Sponsor's control, with access to unblinded data, procedures to ensure maintenance of overall study blinding should be described. The procedure to maintain the blinding when interim analyses are performed should also be explained. DMC (or other committee) composition and operating procedures should be briefly described, and planned DMC (or other committee) monitoring of the results of the study should be described. If the committee charter and meeting minutes are to be included in the CSR, these should be included in an optional appendix, e.g. Appendix 16.1.13. Where appropriate, blinding should be maintained.

Interpretation or observer bias may be introduced if both the Investigator and the subject are not blinded to the treatment being administered and received, respectively. Bias can be introduced if Investigators need to use any form of subjective assessment to obtain a result (such as assessment of a level of severity of an AE) or if the subject is volunteering information (responses to a Quality of Life questionnaire for example). If the study was not blinded then it must be explained why it was felt that the risk of bias was reduced, e.g. use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure, and Holter tapes are often read by automated systems that are presumably immune to observer bias. If blinding was considered desirable but not feasible, the reasons and implications should be discussed. Sometimes blinding is attempted but is known to be imperfect because of obvious drug effects in at least some subjects (e.g. dry mouth, bradycardia, fever, injection site reactions, changes in laboratory data). Such problems or potential problems should be identified and if there were any attempts to assess the magnitude of the problem or manage it (e.g. by having some endpoint measurements carried out by people shielded from information that might reveal treatment assignment), they should be described. In these situations, if Investigational Product cannot be blinded, the blinding of other groups such as data management, statistics and medical writing should have been documented in the clinical study protocol so that decisions could be taken in a blinded manner, reducing the risk of interpretation bias.

For procedures for unblinding in the event of safety need, refer to the protocol (in Appendix 16.1.1).

NOTE: Masking, while often used synonymously with blinding, usually denotes concealing the specific study intervention used and is often preferred to use of the term 'blinding' in the field of ophthalmology (CDISC definition).

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Comment [A155]: ICH E3 text from Section 9.7.1 (Statistical and analytical plans) on the DMC is relocated and integrated more appropriately here (as it is not a statistical method). The ICH E3 text is: 'Planned monitoring of the results of the study should be described. If there was a data monitoring committee, either within or outside the sponsor's control, its composition and operating procedures should be described and procedures to maintain study blinding should be given.'

Comment [A156]: Consider for PPD impact: Data that might identify subjects and names of DMC members are often included in the minutes and charter and since these must not be publicly disclosed, suggest placing them in an optional appendix which will not be publicly disclosed in the 'secondary use CSR'.

In all cases, subject identity and committee member identity must be protected in the 'secondary use CSR'.

Comment [A157]: For clarity, the preceding clause substitutes the omitted ICH E3 text which reads:
'If blinding was considered unnecessary to reduce bias for some or all of the observations, this should be explained'.

Comment [A158]: Suggest procedures for unblinding should accompany the blinding procedures, hence included here.

9.4.4 Selection of Dose(s) and Timing of Dose for Each Subject

The procedures for selecting each subject's dose or dose ranges of Investigational Product should be described.

The timing (time of day, interval) of dosing and the relation of dosing to meals should be described, and if it was not specified, this should be noted.

Any specific instructions to subjects about when or how to take the dose(s) should be described, including those in relation to ingestion of food, posture and the possible effects of concomitant medication/alcohol/caffeine/nicotine.

9.4.5 Treatment Compliance

The measures taken to ensure and document Investigational Product compliance should be described, as per protocol, e.g. drug accountability, diary cards, electronic diaries, electronic Patient-Reported Outcomes (PROs), blood, urine or other body fluid drug level measurements, or medication event monitoring, etc. If drug levels in body fluids have been used to determine compliance, the measurements and methodology used should be described.

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Comment [A159]: ICH E3 Section 9.4.4 (Selection of Doses in the Study) often overlaps with ICH E3 Section 9.4.5 (Selection and Timing of Doses for Each Patient). Recommend merging the content of the two and adapting the title, appropriately, e.g. Selection of Dose(s) and Timing of Dose for Each Subject.

Comment [A160]: The following is relocated from ICH E3 Section 9.4.4 (Selection of Doses in the Study) and integrated more appropriately with content in CORE Reference Section 9.2 (Discussion of study design, including the choice of control groups): '(e.g., prior experience in humans, animal data)'.

Comment [A161]: The following ICH E3 Section 9.4.4 (Selection of Doses in the Study) text is relocated and integrated more appropriately with content in CORE Reference Section 9.2 (Discussion of study design including the choice of control groups): 'These procedures can vary from simple random assignment to a selected fixed drug/dose regimen… Procedures for back-titration, if any, should also be described.'

Comment [A162]: The following ICH E3 Section 9.5.4 (Drug Concentration Measurements) text is relocated here and paraphrased: 'Any relation of drug administration and sampling to ingestion of food, posture and the possible effects of concomitant medication/alcohol/caffeine/nicotine should also be addressed'.

Comment [A163]: ICH E3 Section 9.4.6 (Blinding) content is merged with content on avoidance of bias (Section 9.4.3) and omitted from here.

Comment [A164]: 'Treatment compliance' relates to Investigational Product and therefore sits more logically ahead of 'Prior and Concomitant Therapy'. The suggested running order of ICH E3 content is therefore switched in CORE Reference.

Comment [A165]: See FDA Guidance for Industry. PRO measures: use in medical product development to support labeling claims, Dec 2009: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.
Advise that PROs are either efficacy or safety measures and should be fully integrated into the appropriate efficacy or safety sections of the CSR.

Comment [A166]: Suggest that information on drug concentration measurement and methodology is integrated with content on PK measurements, (see, for example, CORE Reference Section 9.5.3 [Pharmacokinetic and Pharmacodynamic Measurements]), rather than being presented under treatment compliance.

9.4.6 Prior and Concomitant Therapy

Which drugs or procedures were allowed before and during the study, whether and how their use was recorded and any other specific rules and procedures related to permitted or forbidden concomitant treatment, should be described, as per protocol. Often some of the allowed or prohibited prior and concomitant treatments are defined in the inclusion/exclusion criteria.

Consider how the allowed concomitant treatment (including non-Investigational Product treatment if used) might affect the outcome due to either drug-drug interaction or direct effects on the study endpoints, and explain how the independent effects of concomitant and Investigational Product could be ascertained. Any such observed effects should be described in, for example, Section 13 (Discussion and Overall Conclusions).

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Comment [A167]: ICH E3 Section 9.4.5 (Selection and Timing of Doses for Each Patient) is amalgamated with CORE Reference Section 9.4.4 content above and omitted from here.

Comment [A168]: The choice of non-Investigational Product treatment and its regimen (if used) should be described, for example, under Section 9.4.1 (Treatments Administered). This is a reminder to ensure non-Investigational Product treatment is not overlooked.

Comment [A169]: Clarification that some allowed or prohibited prior and concomitant treatments may be defined in the inclusion/exclusion criteria.

Comment [A170]: Suggest to cross reference, for example, Section 9.3 (Selection of Study Population).

Comment [A171]: Clarification to prompt consideration of such treatment effects here (including possible effects of protocol required underlying therapy), and to discuss them in the Discussion if the possible effect is observed.

Comment [A172]: Slight rewording of ICH E3 text in this paragraph with no loss of meaning.

9.5 EFFICACY AND SAFETY VARIABLES

The title of this section (Efficacy and Safety Variables) may be renamed as appropriate to the individual study. For example, if the study measures drug concentration (pharmacokinetics [PK]), pharmacodynamics (PD), including, for example, an exploratory biomarker, or pharmacoeconomic parameters, adapt the title to 'Efficacy, Safety and Other Variables'. 'Other' variables may be specified in the title.

Note that PROs are either efficacy or safety measures and should be fully integrated into the appropriate efficacy or safety sections of the study report.

Clear distinction should be made between variables (defined in this section), objectives (defined in Section 8.1 [Objectives]) and endpoints (defined in Section 8.2 [Endpoints], with endpoint analysis methodology described in Section 9.7 [Statistical Analysis Methods Planned in The Protocol and Determination of Sample Size]). A brief description of measurements relating to each endpoint can be made, for example, in Section 9.5.1, Section 9.5.3 and Section 9.5.4 as applicable.

In summary, an objective is addressed by recording an endpoint. For definitions, see 'Terminology' below.

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Comment [A173]: See ICH E3 Q & A Point 1: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf which states: '*If particular types of information or topics are not addressed in ICH E3 or if their location is not specified, this information or topic should be placed in the section that is most relevant. For example, pharmacokinetic or quality of life results could be placed in appropriately identified sub-sections of the efficacy and safety results sections, or they could be placed in new, appropriately identified results sections.*'

CORE Reference provides a suggested placement that integrates these other types of information. This should not be considered 'the only way'. Adapt the report structure in the way that best suits the study.

Adapt this section title as appropriate to the variables for the study presented within this section. For example, if PK, PD and other variables are included, mention these in the title.

Comment [A174]: **Clarification on general approach to report structuring**:
See ICH E3 2012 Q & A guidance text Points 1 and 4 which clarify that flexibility in the order of presentation of study variables/endpoints is strongly encouraged. For example, if the primary objective of the study is PK/PD, followed by safety objectives, and no efficacy objectives are included in the study, then the logical order of variables would be PK/PD followed by safety variables.

Irrelevant CSR sections may be omitted.

CORE Reference reminder: It should however be noted that statistical output numbering, (traditionally, summary tables numbered 14.x.x and listings numbered 16.2.x.x) may make it preferable not to omit irrelevant sections, but rather mark these as 'not applicable', to ensure no mismatch of CSR section numbers and statistical output numbers. Either approach is acceptable.

The presentational order of study endpoints and variables must flow throughout the CSR, with consistent ordering in the methodological, results and conclusions sections.

Comment [A175]: See FDA Guidance for Industry. PRO measures: use in medical product development to support labeling claims, Dec 2009: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.

Comment [A176]: The Terminology page that follows presents relevant definitions used in CORE Reference. These recommended definitions are based on extensive discussions by the authors of CORE Reference.

Comment [A177]: To address the ambiguity regarding the content required, clarification of terminology and example subheadings for each efficacy and safety assessment are provided below.

Terminology

Term	Definition (modified from CDISC)	Example	2-arm, parallel-group study (Group A: Test Product; Group B: placebo) 8 weeks of randomised treatment	
Objective	The goal a trial is designed to achieve in terms of the scientific questions to be answered		Demonstration of anti-hypertensive efficacy of Test Product	
			Scenario I	**Scenario II**
Hypothesis	Statement relating to the possible different effect of the interventions on an outcome		H_0: The proportion of responders at Week 8 in Group A is lower or equal relative to Group B H_1: The proportion of responders at Week 8 in Group A is higher than in Group B	H_0: The mean change at Week 8 in Group A is equal or greater relative to Group B H_1: The mean change at Week 8 in Group A is lower than in Group B
Measurement	Process of recording the value of a variable (a quantitative value requires a unit; the same value may be expressed in different units [e.g. mg/mL vs. mmol/dL])		Recording of blood pressure (BP) [mmHg]	
Procedure	Specific test carried out on the subject, specimen or data		Sphygmomanometry (common method to measure BP) after 10 minutes in supine position	
Assessment / evaluation	Systematic judgment on the recorded value(s) of a variable. Judgment is based on specific (typically subjective) criteria.		Clinical relevance of diastolic BP values outside of normal ranges at Week 4 and Week 8 (yes/no)	
Variable	A measureable attribute, phenomenon or event that have either qualitative or quantitative values which may be expected to vary over time and within and/or between subjects Note: A variable is an entity to be captured either directly on the CRF or as a derived value (i.e. calculated from other CRF-recorded data).	Recorded (on CRF)	- Diastolic blood pressure at Baseline [mmHg] - Diastolic blood pressure at Week 4 [mmHg] - Diastolic blood pressure at Week 8 [mmHg]	
		Derivation Level 1 (subject level)	- Absolute change in diastolic BP from Baseline to Week 4 [mmHg] - Absolute change in diastolic BP from Baseline to Week 8 [mmHg]	
		Derivation Level 2	(subject level) - Responder* at Week 4 [yes/no] - Responder* at Week 8 [yes/no]	(population level) - ***Mean change in diastolic BP from Baseline to Week 4 [mmHg]*** - ***<u>Mean change in diastolic BP from Baseline to Week 8 [mmHg]</u>***
		Derivation Level 3	(population level) - ***Proportion of responders* at Week 4 [%]*** - ***<u>Proportion of responders* at Week 8 [%]</u>***	*not applicable*
Endpoint	Variable that pertains to an objective of a trial Note: The primary endpoint should be linked to a hypothesis.	Endpoints set in ***bold Italics*** Primary endpoints ***<u>underlined</u>***		

* Response is defined as reduction (relative to Baseline) in diastolic blood pressure ≥ 15 mmHg.

ICH E3 text | *ICH E3 2012 Q&A text* | CORE Reference text | [Right margin comment=RATIONALE]

Comment [A178]: This Terminology page is deliberately not titled 'Table' and is deliberately not numbered because it is **not** an 'Example Table' and should not appear in a CSR.

Comment [A179]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf.

The definition of 'estimand' on slide 8 of the 2015 ICH Presentation: https://www.efspi.org/Documents/Leaders%20Meetings/6th/8.%20Chrissie%20Fletcher%20EFSPI%20Statistics%20Leaders%202015%20estimands.pdf is 'Estimand is defined as "what is to be estimated to address the scientific question posed by a trial".

The authors of CORE Reference interpret that estimand is different from an endpoint which is the variable that pertains to the objective, whereas the estimand considers the endpoint, the population and any intervention effects.

For the example in the Terminology Table, the estimand could be:

'Mean change in diastolic BP from Baseline to Week 8 for subjects who have not discontinued treatment by the Week 8 assessment'.

Comment [A180]: The wording of the objective may be neutral or positive and no convention is mandated. Here the example objective is positive ("demonstrate efficacy") but neutral wording may also be used ("assess efficacy").

9.5.1 Efficacy and Safety Measurements Assessed and Schedule of Assessments

The content may use subheadings. Example subheadings (ordered to reflect the design of the individual study) may include:

9.5.1.1 Primary Efficacy Measurement
9.5.1.2 Secondary Efficacy Measurements
9.5.1.3 Other Efficacy Measurements

Include exploratory measurements.

9.5.1.4 Safety – Adverse Events
9.5.1.5 Safety – Clinical Laboratory Evaluation
9.5.1.6 Safety – Vital Sign Measurements
9.5.1.7 Safety – Physical Examination

The specific efficacy, safety and/or any other variables to be assessed, their schedule (days of study, time of day, relation to meals, and the timing of critical measures in relation to Investigational Product administration, e.g. just prior to next dose, two hours after dose), the methods for measuring them and the persons responsible for the measurements, should be described. If there were known changes in personnel carrying out critical measurements, these should be reported.

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Comment [A181]: ICH E3 uses the term 'flow chart' which may not be as clear as the term 'schedule of assessments', suggested here.

Comment [A182]: This section title should be renamed as appropriate to the individual study design, as explained in Section 9.5 above.

Comment [A183]: **Clarification on general approach to report structuring**: Reminder that flexibility in the order of presentation of study variables/endpoints is strongly encouraged.

The presentational order of study variables/endpoints must flow throughout the CSR, with consistent ordering in the methodological, results and conclusions sections.

Comment [A184]: ICH E3 text: 'The specific efficacy and safety variables to be assessed and laboratory tests to be conducted…' is clarified to prevent the inadvertent omission of any relevant assessment variable.

Comment [A185]: In practice, personnel changes can be difficult to ascertain.

Variable(s) associated with the primary endpoint defined in the protocol (which may be efficacy, safety or any other type of variable, depending on the study) should be clearly specified. If the primary variable is an efficacy variable and if an efficacy threshold was defined in the protocol, this should be described.

If measurements of data relating to study variables were made more than once, the particular measurements (e.g. average of several measurements over the entire study, values at particular times, or last on-therapy value) planned as the basis for comparison of Test Product and Control Product should be specified. If categorical responses (global scales, severity scores, responses of a certain size) were to be used in analysing responses, they should be clearly defined. The use of validated instruments is encouraged.

It is usually helpful to display a Schedule of Assessments in a tabular format (see Example Table 9.1), with the frequency and timing of efficacy and safety measurements, visit numbers and times shown, or, alternatively, times alone can be used (visit numbers alone are more difficult to interpret). Whether any specific instructions (e.g. guidance or use of a diary) to the subjects were used should also be noted. The inclusion of the Schedule of Assessments (Example Table 9.1) means that a detailed list of tests performed at each visit is not required. The Schedule of Assessments from the protocol should be used, where possible.

Any definitions used to characterise outcome (e.g. criteria for determining occurrence of acute myocardial infarction, designation of the location of the infarction, characterisation of a stroke as thrombotic or haemorrhagic, distinction between transient ischaemic attack and stroke, assignment of cause of death) should be explained in full. Any techniques used to standardise or compare results of laboratory tests or other clinical measurements (e.g. electrocardiogram [ECG], chest x-ray) should also be described. This is particularly important in multicentre studies.

If anyone other than the Investigator was responsible for evaluation of clinical outcomes (e.g. the Sponsor or an external committee to review x-rays or ECGs or to determine whether the subject had a stroke, acute infarction, or sudden death), the person or group should be identified. The procedures, including means of maintaining the blind and centralising readings and measurements, should be described fully.

Procedures for AE and SAE reporting should not be described but rather the appropriate protocol section(s) should be referenced, unless it is critical for the understanding of the reporting procedures, e.g. in a complex or unusual study. The means of obtaining AE data should be described (volunteered, checklist or questioning), as should any specific rating scale(s) used and any specifically planned follow-up procedures for AEs or any planned rechallenge procedure.

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Comment [A186]: Primary variable(s) text included in ICH E3 Section 9.5.3 is consolidated here. The ICH E3 text states: 'The primary measurements and endpoints used to determine efficacy should be clearly specified. Although the critical efficacy measurements may seem obvious, when there are multiple variables, or when variables are measured repeatedly, the protocol should identify the primary ones, with an explanation of why they were chosen, or designate the pattern of significant findings or other method of combining information that would be interpreted as supporting efficacy. If the protocol did not identify the primary variables, the study report should explain how these critical variables were selected (e.g. by reference to publications, guidelines or previous actions by regulatory authorities) and when they were identified (i.e. before or after the study was completed and unblinded). If an efficacy threshold was defined in the protocol, this should be described.'

Note the alignment of terminology to 'variable(s) associated with the primary endpoint'. The intention is to limit terminology to objective, endpoint and variable as far as possible. In practice, the primary variable is expected to be protocol-defined, so the text is simplified accordingly.

Comment [A187]: Clarification of ICH E3 term 'critical measurements'.

Comment [A188]: This paragraph of text is relocated from ICH E3 Section 9.7.1 (Statistical and analytical plans) as it refers to endpoint derivation detail rather than analysis methods.

Comment [A189]: ICH E3 text: '…graphically in a flow chart (see Annex III of the guideline)…' is substituted.

Comment [A190]: ICH E3 uses 'blindness'. Language adapted to 'the blind' for clarity.

Comment [A191]: It is suggested that these complete procedures are addressed with content in, for example, Section 9.4.3 (Avoidance of Bias).

Comment [A192]: Clarification to guide that a cross-reference to the protocol rather than in-text CSR presentation is suggested because AE/SAE reporting procedures are generally standard in most studies. Direct descriptions of these procedures in the text of the CSR are not necessary, except for exceptional circumstances, e.g. in case the protocol is not clear about these procedures or if the reporting procedures changed during the course of the study.

Any rating of AEs by the Investigator, Sponsor or external group (e.g. rating by severity or likelihood of drug causation) should be described. The criteria for such ratings, if any, should be given and the parties responsible for the ratings should be clearly identified. If efficacy or safety was to be assessed in terms of categorical ratings, numerical scores, etc. the criteria used for point assignment (e.g. definitions of point scores) should be provided. For multicentre studies, indicate how methods were standardised.

Example Table 9.1 Schedule of Study Events and Assessments in Protocol xxx

Assessment	Screen[a]	Treat-ment Day 1	Evaluations (Week Number) 1	2	4	8 or 12	Termin-ation[b]
Visit	1	2	2	3	4	5	6
Informed Consent	X						
Inclusion/Exclusion	X	X					
Medical History	X	X					
Pregnancy Test	X						
Vital Signs	X	X		X	X	X	X
Physical Examination	X	X[c]					X
Neurological Examination	X						X
Laboratory Tests	X				X		X[d]
Serum Samples	X				X		X[d]
Concomitant Medications	X	X		X	X	X	X
Efficacy Assessment 1	X	X		X	X	X	X
Efficacy Assessment 2	X	X		X	X	X	X
Efficacy Assessment 3[e]		X[f]		X	X	X	X
Adverse Events		X	X	X	X	X	X
Phone Call			X				

[a] The screening examination occurred within two weeks before injection.
[b] The termination visit occurred when clinical benefit ceased or four months after the injection (Week 16).
[c] Only additional information noted since screening was recorded (using the screening CRFs).
[d] The procedure was performed only if the termination visit occurred prior to or in place of the Week 4 visit.
[e] Assessments were made separately by the Investigator and the subject.
[f] The baseline assessment consisted of notes taken by the Investigator only; the purpose was to provide a reference for future assessments.

9.5.2 Appropriateness of Measurements

The use of standard validated instruments should be documented.

If any of the efficacy or safety assessments or instruments were not standard, i.e. widely used and generally recognised as reliable, accurate, and relevant (able to discriminate between effective and ineffective agents), its reliability, accuracy and relevance should be documented. It may be helpful to describe alternatives considered but rejected. If these

Comment [A193]: For submissions in the US, FDA holds that the Sponsor (rather than Investigator) should make final decisions on causality given their access to a complete dataset of safety data across multiple sites. See New England Journal of Medicine (NEJM) Perspective article from key FDA Center for Drug Evaluation and Research (CDER) leaders: http://www.nejm.org/doi/full/10.1056/NEJMp1103464 that explains the reporting regulation [21 CFR 312.32 (c) (A)]: http://www.ecfr.gov/cgi-bin/text-idx?SID=9661aeb85e493caed76a11faa6545dce&mc=true&node=se21.5.312_132&rgn=div8 associated with the (at that time) new requirements for clinical trial safety reports.

Comment [A194]: Example Table 9.1 combines and streamlines the information presented in ICH E3 Annex IIIa and IIIb, both of which are examples titled 'Study Design and Schedule of Assessments'.

Comment [A195]: Suggest to include protocol number in table title to aid regulatory reviewers who often copy and paste key CSR information into their own summary documents.

Comment [A196]: Clarification to include description of the use of validated instruments which is not included in ICH E3.

were discussed and agreed *a priori* with the regulators, this should be noted, with reference to date of meeting/discussion. If a surrogate endpoint (a laboratory measurement or physical measurement or sign that is not a direct measure of clinical benefit) was used as a study endpoint, this should be justified, e.g. by reference to clinical data, publications, guidelines or previous actions by regulatory authorities.

9.5.3 Pharmacokinetic and Pharmacodynamic Measurements

9.5.3.1 Pharmacokinetic Measurements

Any drug concentration measurements, and the sample collection times and periods in relation to the timing of drug administration, should be described. Permitted time deviation(s) in PK blood sample collection from the planned time schedule should also be described for the PK studies. Any relation of sampling to ingestion of food, posture and the possible effects of concomitant medication/alcohol/caffeine/nicotine should also be addressed. The biological sample measured, the handling of samples and the method of measurement used should be described, referring to published and/or internal assay validation documentation for methodological details. Where other factors are believed important in assessing PK (e.g. soluble circulating receptors, renal or hepatic function), the timing and plans to measure these factors should also be specified.

9.5.3.2 Pharmacokinetic Parameters

Include details of parameters measured: area under the curve (AUC), maximum plasma concentration (C_{max}), etc., if applicable.

9.5.3.3 Pharmacodynamic Measurements

Include PD and/or biomarker measurements if applicable.

Pharmacodynamics is a branch of pharmacology that studies reactions between drugs and living structures, including the physiological responses to pharmacological, biochemical, physiological, and therapeutic agents (CDISC definition).

The PD measurement may be a biomarker, which can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention (National Institutes of Health [NIH] definition). This includes pharmacogenomic assessments to determine any variations of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) characteristics as related to drug response.

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Comment [A197]: Scientific advice meeting (in EU) or FDA discussions (in US) where regulatory authority advice is sought on protocol design are typically when these types of issues would be addressed.

Comment [A198]: Suggest the omission of ICH E3 Section 9.5.3 (Primary Efficacy Variable) and inclusion of the relevant consolidated information into CORE Reference Section 9.5.1 content above.

Comment [A199]: Suggest to amend title of ICH E3 section 9.5.4 'Drug Concentration Measurements' for clarity as drug concentration measurements are the same as PK (and sometimes PD) measurements, but the exclusion of these terms from the section title may cause doubt.

Comment [A200]: Section title is further adapted to allow for presentation of PD measurements.

Comment [A201]: A sub-section is suggested for summary of the raw data (PK measurements).

Comment [A202]: ICH E3 text 'to be measured' is clarified as 'measurements'.

Comment [A203]: ICH E3 text states 'Any relation of drug administration and sampling…' The reference to drug administration is omitted as it is misplaced in this section. This detail for Investigational Product administration is more appropriately added to dose and timing content, in for example, Section 9.4.4 instead.

Comment [A204]: 'Parameters' is typically used in the area of PK. Alternative language choices should be based on consultation with the PK expert.

Comment [A205]: A sub-section is suggested for capturing a summary of PK parameters (area under the curve, maximum concentration, etc).

Comment [A206]: Definition is included for clarity.

Comment [A207]: Definition is included for clarity.

Where PD measurements, such as biomarkers or pharmacogenomic assessments, are made, the sample collection times and periods in relation to the timing of drug administration, should be described. The biological sample measured, the handling of samples (including coding) and the method of measurement used should be described, referring to published and/or internal assay validation documentation for methodological details. Where other factors are believed to be important in assessing the PD observation (e.g. drug concentration, metabolites, isomers and finished products), the timing and plans to measure these factors should also be specified.

9.5.3.4 Pharmacodynamic Parameters
Include details of PD parameters measured, if applicable.

9.5.4 Other Measurements

Include details of other study-specific measurements (for example, quality of life and pharmacoeconomic measurements, and also pharmacogenomics if not included under the CSR text on PD) if applicable.

9.6 DATA QUALITY ASSURANCE

The quality assurance (QA) and quality control (QC) systems implemented to assure the quality of the data should be described in brief. Describe the quality management approach implemented in the study and summarise important deviations from the predefined quality tolerance limits described in the quality management system for the study.

Any steps taken at the investigation site or centrally to ensure the use of standard terminology and the collection of accurate, consistent, complete and reliable data, such as training sessions, monitoring of Investigators by Sponsor personnel, instruction manuals, data verification, cross-checking, use of a central laboratory for certain tests, centralised ECG reading or data audits, should be described. It should be noted whether Investigator meetings or other steps were taken to prepare Investigators and standardise performance.

Documentation of inter-laboratory standardisation methods and laboratory QA procedures, if used, should be provided in Appendix 16.1.10. Laboratory manuals should not be included. Laboratory standardisation methods and laboratory QA procedures include laboratory validation procedures and/or certificates, equipment calibration, internal QC or external QA procedures.

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Comment [A208]: Addition of examples that are relevant for PD observation.

Comment [A209]: These are the requirements in ICH E3 for PK (starting with the text '…the sample collection times…' to the end of the paragraph) so logically these should also apply to PD - and are therefore included here.

Comment [A210]: Suggest inclusion of optional section to include 'other measurements' that may include quality of life, pharmacoeconomic or other measurements.

Comment [A211]: ICH E15 Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories Step 4, 1 Nov 2007 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E15/Step4/E15_Guideline.pdf.

Comment [A212]: **Awareness comment pending finalisation of ICH guidance:**
ICH E3 text 'If none were used, this should be stated.' is omitted from here due to requirement of a risk-based quality management system for all trials, as described in:
Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) - Step 2 (Draft) dated 11 June 2015 (note that Step 4 [Final] is expected in November 2016):
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf.
Addendum **Section 5.0 Quality Management** states 'The sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials…' and describes the risk-based approach needed for the quality management system which comprises:
- Critical process and data identification
- Risk identification
- Risk evaluation
- Risk control
- Risk communication
- Risk review
- Risk reporting.

Addendum Section 5.0.7 Risk Reporting states 'The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance)'.

Comment [A213]: Text addition to capture the E6 Addendum requirement described above. Note that the ICH E3 and CORE Reference text below may be covered in the quality management approach.

Comment [A214]: Suggest that laboratory standardisation methods and QA procedures be further defined in the CSR so have suggested required content of Appendix 16.1.10, and relocated the text to follow the 'steps taken' paragraph.

The date of database release may be included.

The assurance of overall quality for the study is through audit. If the Sponsor used an independent internal or external auditing procedure, it should be mentioned here and described in Appendix 16.1.8; and audit certificates from each audit, if *applicable* and available, *may* be provided in Appendix 16.1.8 (note it is not necessary to include audit report[s] in Appendix 16.1.8).

9.7 STATISTICAL ANALYSIS METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical Plans

The statistical analyses planned in the protocol and any changes made before outcome results were available should be described. These will have been described in further detail in the final statistical analysis plan (SAP). In this section (Section 9.7), emphasis should be on which analyses, comparisons and statistical tests were planned, not on the ones that were actually used. Planned methods in this context means all methods described in the final SAP.

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Comment [A215]: Especially for studies with multiple consecutive analyses and reports, suggest to include which cut-off date(s) is (are) used for the analyses reported (e.g. date of database release).

This key information is also recommended for placement in the Introduction.

Comment [A216]: ICH E3 2012 Q & A reminds that per ICH GCP, audit certificates should be provided when required by applicable law or regulation - this is region and/or country-specific.

Comment [A217]: Per ICH E3 2012 Q & A Point 3: '*Certain documents may be required for the CSR by individual countries or regions, in which case they should be included. For example, according to ICH-GCP, an audit certificate (16.1.8) should be provided when required by applicable law or regulation. If there is any uncertainty about whether documents should be included or not, the appropriate regulatory agency may be consulted.*' it is suggested that if audit certificates are in the TMF, they need not be replicated in the CSR appendix, unless there is a specific country requirement to do so.

Comment [A218]: Clarification that audit **reports** are not to be included in Appendix 16.1.8, only audit certificates.

Comment [A219]: Quality assurance procedures in relation to the entire study are missing from ICH E3, so this, as well as a more detailed explanation of audits is included.

Comment [A220]: Analytical plans are usually described in the PK section. Section title is adjusted to better reflect the general content of this section, with adaptation to use the word 'analysis'.

Comment [A221]: Omitted the ICH E3 word 'analytical' before plans to better reflect the general content of this section.

Comment [A222]: The paragraph of text in ICH E3 Section 9.7.1 which refers to endpoint derivation detail has been omitted from here and integrated with CORE Reference content in Section 9.5.1 (Efficacy and Safety Measurements Assessed and Schedule of Assessments) as it is deemed endpoint derivation detail rather than analysis methods.

Comment [A223]: ICH E3 text does not explain the development of statistical analysis planning from the protocol to the SAP.

Comment [A224]: ICH E3 text 'which ones were' is clarified as 'the ones that were'.

The final SAP will have incorporated any changes covered by protocol amendments and any changes to planned analyses made prior to study unblinding that were not considered to require a protocol amendment.

The following example subheadings may be used:

9.7.1.1 General Approaches

9.7.1.2 Primary Efficacy Endpoint Methodology

Include the methodology for the primary analysis, which may also include methods for sensitivity analyses of the primary endpoint.

9.7.1.3 Secondary Efficacy Endpoint Methodology

9.7.1.4 Other Efficacy Endpoint Methodology

If applicable also include the methodology for exploratory endpoint(s).

9.7.1.5 Safety Endpoint Methodology

9.7.1.6 Pharmacokinetic and Pharmacodynamic Endpoints Methodology

Include if applicable.

9.7.1.7 Other Endpoint Methodology

Include if applicable.

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Comment [A225]: Further detail is added to clarify what is meant by the statistical analyses and tests that were planned (as mentioned in ICH E3 text above), and that changes to analyses agreed prior to study unblinding are considered 'planned analyses'. All this detail should be included in the SAP, which is again referenced.

The description of these changes should be placed in, for example, Section 9.8 (Changes in the Conduct of the Study and Planned Analyses).

Comment [A226]: Suggested subheadings are based on the sections commonly used in SAPs regarding statistical methodology, and matched to Section 9.5 (Efficacy and Safety Variables) subheadings. It is clarified that the information in these example sub-sections should relate to statistical methodologies.

Comment [A227]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf which generally provides detailed guidance for 'An improved framework …[to] focus the sensitivity analyses…' (mid page 4); discuses some types of supportive analyses (start page 5) and states in 'Background to the Proposal' that 'Reporting results from sensitivity analyses is relevant for ICH E3' (start page 5).'

Such analysis aspects are expected to be considered at the study design stage, may be described in the protocol and/or SAP, and should be considered for inclusion in this section if applicable to individual study design, and if available.

Comment [A228]: The definition of a treatment-emergent AE (TEAE) should be included within the content of this section.

Comment [A229]: Suggest that this text is sub-sectioned to match the safety sub-sections in, for example, Section 9.5.1 (Efficacy and Safety Measurements Assessed and Schedule of Assessments).

The final SAP text should be used to place the study results in statistical context.

If more than one analytical approach is plausible, e.g. changes from baseline response, slope analysis, life table analysis, the planned approach should be identified. Also, whether the analyses are to include adjustment for covariates should be specified.

Methodologies described in the final SAP to deal with statistical issues should be included. These may be related to one or more than one endpoint. If those methodologies were implemented or revised after the final SAP, they should be addressed together with changes in the conduct of the study or planned analyses.

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Comment [A230]: Clarification to indicate the text is always sourced from the SAP. ICH E3 does not explicitly state this.

Comment [A231]: Suggest using the SAP text to populate the CSR text in Section 9.7.1 (Statistical Plans). The final SAP (in Appendix 16.1.9) should also be cross-referenced.
A suggested approach is that a brief description of each endpoint can precede the details of the planned statistical analysis methods or an appropriate cross-reference can be made to, for example, Section 8.2 (Endpoints), as required. Statistical methodologies should be described for all planned analyses, with a cross-reference to, for example, Section 9.8 (Changes in the Conduct of the Study or Planned Analyses), or as applicable; brief descriptions can also be included for methods of summarising data.

Comment [A232]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf

Estimands are expected to be considered at the study design stage, may be described in the protocol and/or SAP, and should be considered for inclusion in this section or a cross-reference may be added to Section 8 (Study Objectives and Endpoints) and Section 9.2 (Discussion of Study Design Including the Choice of Control Groups), as applicable.

Comment [A233]: ICH E3 text: 'If critical measurements were made more than once, the particular measurements (e.g. average of several measurements over the entire study, values at particular times, values only from study completers, or last on-therapy value) planned as the basis for comparison of test drug/investigational product and control should be specified' is relocated from here to Section 9.5 because it refers to endpoint derivation detail rather than analysis methods.

Comment [A234]: ICH E3 text: 'If there were any planned reasons for excluding from analysis patients for whom data are available, these should be described. If there were any subgroups whose results were to be examined separately, these should be identified' is subordinated (see 'Examination of subgroups' below).

Comment [A235]: Text relocated here from ICH E3 Section 11 (because this paraphrases 11.4.2 of ICH E3 it is shaded as ICH E3 text) as it deals with methods for dealing with statistical issues.

Comment [A236]: ICH E3 integrates statistical methodological text and statistical results-related text and presents within a single location Section 11.4.2 (Statistical/analytical issues).
The text is actually more logically separated so the methodological text sits here, and the results-related text sits in Section 11.
See comments below for specific details of relocated text.

Method(s) for Statistical Issues Encountered During the Analysis

Adjustments for Covariates:
Methods for selection of, and adjustments for, demographic or baseline measurements or prior treatment, or any other covariate or prognostic factor, including stratification factors used in the randomisation, should be explained.

Handling of Withdrawals, Discontinuations and Missing Data:
The results of a clinical trial should be assessed not only for the subset of patients who completed the study, but also for the entire patient population as randomised or at least for all those with any on-study measurements. Several factors need to be considered and compared for the treatment groups in analysing the effects of withdrawals or discontinuations: the reasons for the withdrawals or discontinuations, the time to withdrawal or discontinuation, and the proportion of withdrawals or discontinuations among treatment groups at various time points. Planned methodologies for assessing time to withdrawal or discontinuation, such as survival data methods, should be explained.

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Comment [A237]: A header, or a statement - to remind that methods only (not results) are presented - may be useful.

Comment [A238]: ICH E3 text: 'The statistical analysis used should be described for clinical and statistical reviewers in the text of the report, with detailed documentation of statistical methods presented in Appendix 16.1.9. Important features of the analysis including the particular methods used, adjustments made for demographic or baseline measurements or concomitant therapy, handling of dropouts and missing data, adjustments for multiple comparisons, special analyses of multicentre studies, and adjustments for interim analyses, should be discussed. Any changes in the analysis made after blind breaking should be identified. In addition to the general discussion the following specific issues should be addressed (unless not applicable)' is relocated to, and modified in CORE Reference Section 11.2 where the results content for these issues are described.

Comment [A239]: ICH E3 text includes concomitant therapy as a possible covariate but this would be a post-baseline measurement. Replaced 'concomitant therapy' with 'prior treatment' as a possible covariate since covariates should be pre-dosing measurements. Reference ICH E9: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf Section 5.7 "It is not advisable to adjust the main analyses for covariates measured after randomisation because they may be affected by the treatments."

Comment [A240]: Clarified that stratification factors may be covariates requiring discussion.

Comment [A241]: Statistical issues methodological text is consolidated and relocated here from ICH E3 Section 11.4.2.1.

Comment [A242]: ICH E3 text 'Although not part of the individual study report, comparisons of covariate adjustments and prognostic factors across individual studies may be an informative analysis in a summary of clinical efficacy data.' is omitted as this is not relevant for the CSR.

Comment [A243]: Clarification of terminology for consistent use of withdrawal and discontinuation, because in practice, the term used in ICH E3 i.e. dropout, is often used in relation to the sample size calculation (dropout rate).

Comment [A244]: ICH E3 text is relocated here from Section 11.4.2.2 (Handling of Dropouts or Missing Data) because this describes the methodology rather than results.

Comment [A245]: Inclusion of such data methods as not covered by ICH E3.

Planned methods for dealing with missing data, e.g. use of estimated or derived data, should be described. Detailed explanation should be provided as to how such estimations or derivations were done and what underlying assumptions were made (see 'Guideline on Missing Data in Confirmatory Clinical Trials', EMA/CPMP/EWP/1776/99 Rev. 1: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf).

Interim Analyses and Data Monitoring:
The process of examining and analysing data accumulating in a clinical trial, either formally or informally, can introduce bias and/or increase Type I error. Therefore, all interim analyses, formal or informal, pre-planned or ad-hoc, by Sponsor/designee or data monitoring group should be described in full, even if the treatment groups were not identified. The methodologies include frequency and nature of any planned interim analysis, including "cut-off date(s)", any specified circumstances under which the study would be terminated and any statistical adjustments to be employed because of interim analyses. Any operating instructions or procedures used for such interim analyses should be described, with particular reference to how it was ensured that only those conducting the interim analysis were unblinded.

The minutes of meetings of any data monitoring group and any data reports reviewed at those meetings, particularly a meeting that led to a change in the protocol or early termination of the study, may be helpful and should be provided in the appropriate appendix. Data monitoring conducted on blinded data should also be described, even if this kind of monitoring is considered to cause no increase in Type I error.

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Comment [A246]: **Awareness comment pending finalisation of ICH guidance:** Final concept paper E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf states 'A clear definition of an estimand is important not only so that the analysis can be pre-specified in all main aspects, but also since the choice of estimand is linked to important considerations around trial design, conduct and analysis. These include, for example, duration of patient follow-up, adherence to randomised treatment, use of alternative medications after discontinuation of randomised treatment and methods to handle missing data in the statistical analysis.'
This is expected to be considered at the study design stage, may be described in the protocol and/or SAP, and should be considered for inclusion in this section, if available.

Comment [A247]: Statistical issues methodological text is relocated here from ICH E3 Section 11.4.2.2 (Handling of Dropoputs or Missing Data) final paragraph. The ICH E3 text 'procedures' is clarified as 'Planned methods'.

Comment [A248]: ICH E3 text refers to analysis performed by a 'study participant'. This wording is misleading (this could read as if a subject in the study could perform analyses) and is clarified.

Comment [A249]: Statistical issues methodological text relocated here from Section 11 (paraphrases ICH E3 Section 11.4.2.3) - the slight adjustment to text is to clarify that the focus here is methodology (Section 11 focus is results).

Comment [A250]: ICH E3 text relocated here from ICH E3 Section 11.4.2.3 (Interim Analyses and Data Monitoring) as this relates to methodology, not results. Minor text edits do not change the meaning, so all text is shaded as ICH E3 text.

Comment [A251]: Suggest to present methodologies in this section, and present the results of such analyses in Section 11.2.3 (Interim Analyses and Data Monitoring).

Comment [A252]: ICH E3 text does not provide context for the 'operating instructions or procedures'. Clarification is added in this regard.

Comment [A253]: Suggest in Appendix 16.1.13.

Comment [A254]: ICH E3 phraseology 'without codebreaking' is standardised.

Comment [A255]: ICH E3 text relocated from Section 11.4.2.3 (Interim Analyses and Data Monitoring) as relates to methodology.

Multicentre Studies:
A multicentre study is a single study under a common protocol, involving more than one centre (e.g. clinics, practices, hospitals) where the data collected are intended to be analysed as a whole (as opposed to a *post-hoc* decision to combine data or results from separate studies). The planned methods such as inclusion of centre and treatment-by-centre interactions in statistical models should be presented.

Multiple Comparison/Multiplicity:
False positive findings increase in number as the number of significance tests (number of comparisons) performed increases. If there was more than one primary endpoint (outcome variable), more than one analysis of particular endpoint, or if there were multiple treatment groups or subsets of the subject population being examined, the statistical analysis should reflect awareness of this and either explain the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary. These methodologies can be presented.

Examination of Subgroups:
If there were any planned reasons for excluding subjects for whom data are available from analysis, these should be described. If there were any subgroups whose results were to be examined separately, these should be identified.

Appendix 16.1.9 should describe all analysis methods used (whether planned or *post-hoc*) in full detail, again clearly identifying those that were *post-hoc*.

Annex IV and Appendix 16.1.9 give further guidance on the content of this section.

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Comment [A256]: '… more than one' replaces ICH E3 text of 'several' as the correct definition of multicentre is 'more than one centre'.

Comment [A257]: ICH E3 instructional text is consolidated to remove duplicate statements about presenting data by centre.

Comment [A258]: ICH E3 text relocated here from ICH E3 Section 11.4.2.4 (Multicentre Studies) as relates to methodology and not to results.

Comment [A259]: Text relocated here from ICH E3 Section 11.4.2.5 (Multiple Comparisons/Multiplicity) as this relates to methodology and not results.

Comment [A260]: Clarified to indicate that multiple testing should be described as part of the methods of analysis of primary endpoint(s).

Comment [A261]: Include these if not already presented in the methods for analysing primary endpoint(s).

Comment [A262]: Added existing ICH E3 subheading from ICH E3 Section 11.4.2.8 for clarification of topic.

Comment [A263]: ICH E3 text surrounding the role of the DMC has been relocated from here to Section 9.4.3.2 (Blinding and unblinding) as it is not deemed to be statistical methods.

Comment [A264]: ICH E3 Section 9.7.1 moved from here: 'If categorical responses (global scales, severity scores, responses of a certain size) were to be used in analysing responses, they should be clearly defined' because detailed descriptions of the variables/endpoints are actually covered in the SAP.

Comment [A265]: As suggested in Section 11.1, placement of *post-hoc* analyses – either embedded in efficacy sections with clear indication they are post-hoc, or presented in a separate section, or appended – will be study-specific. Align the *post-hoc* analysis methods with the *post-hoc* results presentation.

Comment [A266]: Do not overlook ICH E3 Annex VIII/CORE Reference Annex IV for SAP authoring.

Annexes are located towards the end of CORE Reference.

9.7.2 Determination of Sample Size

The planned sample size and the basis for it, such as statistical considerations or practical limitations, should be provided (summarised from the protocol and/or final SAP). Methods for sample size calculation should be given together with their derivations or source of reference. Estimates used in the calculations should be given and explanations provided as to how they were obtained. For a study intended to show a difference between treatments, the difference the study is designed to detect should be specified. For a positive control study intended to show that a new therapy is at least as effective as the standard therapy, the sample size determination should specify the difference between treatments that would be considered unacceptably large and therefore the difference the study is designed to be able to exclude. The power needed for the study may also be stated.

Comment [A267]: Clarification added to state that the protocol **and** final SAP are valid sources of sample size text.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any change in the conduct of the study or planned analyses implemented after the start of the study, should be summarised (with reference to the protocol amendments and SAP for more detailed descriptions) and clear distinction made in every section of the report between procedures or analysis methods planned in the protocol versus amendments or additions. In general, changes made prior to breaking the blind have limited implications for study interpretation. It is therefore particularly critical that the timing of changes relative to blind breaking and availability of outcome results are also well characterised. Changes in conduct of the study and changes in planned analyses should be described, for example, in Section 9.8.1 (Changes in the Conduct of the Study) and Section 9.8.2 (Changes in the Planned Analyses), respectively. Changes made after study unblinding should be described separately.

Comment [A268]: Suggest to summarise to avoid lengthy description in the CSR text.

The detail given in ICH E3 has been partly relocated to Sections 9.8.1 through 9.8.3, with clarifications.

Comment [A269]: Protocol amendments and the 'Changes From The Protocol' section of the SAP could be referenced for more detailed descriptions.

Comment [A270]: ICH E3 text: 'In every section of the report, a clear distinction between conditions (procedures) planned in the protocol and amendments or additions should be made' is paraphrased here.

Comment [A271]: Suggest sub-sections to separate accounting of protocol amendments (Section 9.8.1) from SAP amendments (Section 9.8.2), and clarification to better define chronology with respect to database lock. Presentation in this suggested format means that SAP changes are less likely to be overlooked.

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9.8.1 Changes in the Conduct of the Study

Changes in the conduct of the study can include, but are not limited to, dropping a treatment group, changes in entry criteria or drug (Investigational Product or non-Investigational Product treatment) dosages, adjusting the sample size, and changes in assessment schedules. These changes would require a protocol amendment and can therefore be cross-referenced to the summary of protocol amendment changes, often included in Appendix 16.1.1, to avoid duplication. If a summary of the change is included in the CSR text, the following information should be included: details of the change(s) and the time(s) and reason(s) for the change(s), with a cross-reference, for example to the Appendix 16.1.1 protocol amendment(s) for further details. In the event any changes were made to the study conduct without a corresponding protocol amendment, then this summary should also include why it was agreed not to amend the study protocol and who approved this decision. Personnel changes do not need to be included. It is expected that changes in study conduct would be made while the study is still blinded but this should be corroborated and confirmed in the CSR text.

Any possible implications of the change(s) for the interpretation of the study should be discussed briefly in this section and more fully in other appropriate sections of the report.

9.8.2 Changes in the Planned Analyses

Changes in the planned analyses may have been included in a protocol amendment, in which case they may be handled as described for example, in Section 9.8.1 (Changes in the Conduct of the Study). If changes were made to the analyses planned in the protocol but a protocol amendment was not required, then the changes should have been documented in a separate section of the final SAP entitled for example, 'Changes from the planned analyses'. Those changes can be described using the suggestions made in Section 9.8 (Changes in the Conduct of the Study or Planned Analyses). In the case of changes to analyses documented in a protocol amendment or in the final SAP, the CSR text must state whether these changes were made based on blinded or unblinded data. Protocol amendments and SAPs must be final prior to study unblinding, although decisions to change planned analyses may have been made based on results from unblinded interim analyses. Timing of events must be described with clarity.

9.8.3 Changes Following Study Unblinding and *Post-hoc* Analyses

Changes made to the planned analyses after study unblinding should be avoided due to the impact of bias on results. If assumptions about the study data have not been met then alternative analyses to be used in that situation should have been described in the final SAP. Any other changes made to the planned analyses following study unblinding should be documented appropriately (e.g. SAP addendum, SAP amendment etc.) and described in the CSR text, noting that all results from these analyses must be interpreted with caution due to the decision to change the methods having been taken after study unblinding. Alternative analyses should generally be supplemental to, rather than in place of, the originally planned analysis.

Comment [A272]: ICH E3 text states 'In every section of the report, a clear distinction between conditions (procedures) planned in the protocol and amendments or additions should be made'. This is adequately covered by cross-referencing to a summary of the changes generally. Only key procedures or analyses which changed from the original protocol may be briefly referred to in Section 9 if this adds clarity.

Comment [A273]: ICH E3 requires 'The time(s) and reason(s) for the change(s), the procedure used to decide on the change(s), the person(s) or group(s) responsible for the change(s) and the nature and content of the data available (and to whom they were available) when the change was made should also be described'.
This amount of detail is unnecessary in the CSR; a cross-reference to further (protocol amendment) detail is adequate.

Comment [A274]: Summary of changes from protocol amendments may be replicated here though are often included in Appendix 16.1.1. The amendment summaries may be long and may interrupt the CSR flow. Clarification has been added to optionally cross-reference to Appendix 16.1.1 for summary of amendment changes.

Comment [A275]: ICH E3 text states: '…whether the change was documented as a formal protocol amendment or not'. Clarification is provided about detail that should be presented in such cases.

Consider for PPD impact: The name(s) of those involved in the decision-making process for change(s) not covered by protocol amendment(s) - if not the PI or CI - may need to be considered for redaction in the 'secondary use CSR' for public disclosure.

Comment [A276]: ICH E3 text states 'In general, changes made prior to breaking the blind have limited implications for study interpretation. It is therefore particularly critical that the timing of changes relative to blind breaking and availability of outcome results be well characterised'. This text is consolidated in the sentence here.

Comment [A277]: Changes in planned analyses are separated from changes in conduct for the study above, for added clarity.

Comment [A278]: A separate sub-section for post-unblinding changes and *post-hoc* analyses (Section 9.8.3) is suggested to detail those unplanned analyses which should **not** be confused with the preplanned main analyses.
This makes a distinction between analysis methods planned with the study blind intact and analyses conducted post unblinding, the results of which are potentially subject to a far higher degree of bias. Two distinct sections are recommended in the interest of transparency.

Comment [A279]: 'Post-hoc Analyses' may be omitted from the title of this section as appropriate.

If *post-hoc* analyses (e.g. exploration of sub-groups of data not previously planned) were conducted, the statistical methods should be summarised and the results presented, for example, in Section 11 (Efficacy and Other Evaluations). Alternatively, *post-hoc* analyses may only be included in Appendix 16.1.9. The CSR text must note that results from these analyses should be interpreted with caution as the analysis methods were not pre-specified prior to study unblinding.

Comment [A280]: Suggest that in such cases, a cross-reference is provided in the CSR text to Appendix 16.1.9.

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10. STUDY SUBJECTS

General notes for all results sections: The CSR text should present the results from the statistical outputs. When extracting results from a larger end-text table into an in-text table, care must be taken not to omit any information that would change the interpretation of the results. In general, do not repeat in-text tabulated summary data by additionally describing it in text.

If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

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Comment [A281]: Consider for PPD impact: All aggregated data in the 'primary use CSR' should be evaluated for possible redaction in the 'secondary use CSR' for public disclosure. See Preface for explanation about the risk of de-anonymisation from aggregated data.

Comment [A282]: In ICH E3, much of the instruction pertaining to listings creation is embedded in separate sub-sections of the results section of the guideline. However, these instructions are actually applicable to all data listings presentations. The content has been drawn together and presented directly before the 'Explanation of Annexes' section (towards the end of CORE Reference) for clarity.

Comment [A283]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.
Note that the CORE Reference assumption is that data including, for example, patient identification numbers, are not proactively anonymised. However, if proactively anonymised data has been used to author the 'primary use CSR', then certain redactions may not be necessary in the 'secondary use CSR' for public disclosure.
See, for example, Pharmaceutical Users Software Exchange (PhUSE) De-Identification Working Group, "De-Identification Standards for CDISC SDTM 3.2," 2015 (http://www.phuse.eu/Data_Transparency_download.aspx) for listed direct and quasi identifiers potentially found in clinical data, and that can facilitate identification of variables in clinical reports.

Comment [A284]: Consider for PPD impact: Subject numbers may be created using a centre identifier component. Subject re-identification, particularly for centres entering small numbers of study subjects, may be possible through a subject number that includes a centre identifier component. Where individual subject numbers are presented in the 'primary use CSR', it is recommended that these are fully redacted in the 'secondary use CSR' for public disclosure. In all cases, the entire subject number - including any centre identifier component – should be redacted.

Comment [A285]: Consider for PPD impact: See March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf).
This guidance is composed of procedural aspects, anonymisation of personal data and redaction of CCI.
Chapter 3, Section 5 (EMA recommendations to MAHs/applicants on how best to achieve anonymisation) supports the general approaches to presentation of subject level information suggested in CORE Reference.

10.1 DISPOSITION OF SUBJECTS

Study enrolment is the entry of a subject into a clinical trial, usually following the signing of the informed consent form, although in some cases, this may be study-specific. Once a subject has been enrolled, the protocol applies to that subject. Study randomisation requires assignment to an intervention. "Withdrawal" is applied to withdrawal from treatment and protocol-defined procedures; "discontinuation" is applied to stopping of treatment only.

There should be a clear accounting of all subjects who entered the study, using figures or tables in the text of the report. The numbers of subjects who were randomised and who entered and completed each phase of the study (or each week/month of the study), should be provided, as well as the reasons for all post-randomisation discontinuations and withdrawals, grouped by treatment and by major reason (AE, unsatisfactory efficacy response, failure to return, lost to follow-up, etc.). A clear distinction should be made between discontinuations (i.e. stop treatment), where the subject remains in the study and completes some or all of the protocol-defined procedures, and withdrawals (i.e. stop treatment and stop all protocol-defined procedures) from the study, where no further information is collected on the subject. Whether subjects are followed for the duration of the study, even if Investigational Product is discontinued, should be made clear. It may also be relevant to provide the number of subjects screened for inclusion and a breakdown of the reasons for excluding subjects during screening, if this could help clarify the appropriate subject population for eventual drug use. A flow chart or table is often helpful and should be included (see Example Figure 10.1).

In Appendix 16.2.1, there should also be a listing of all subjects who were withdrawn from the study and subjects who discontinued Investigational Product after enrolment, broken down by centre and treatment group, giving a subject identifier, the specific reason for discontinuation, the treatment (Investigational Product and dose), cumulative dose (where appropriate) and the duration of treatment before discontinuation. Whether or not the blind for the subject was broken at the time of discontinuation should be noted. It may also be useful to include other information, such as critical demographic data (e.g. age, sex, race), concomitant medication and the major response variable(s) at termination. See Annex II for an example of such a listing.

<Deliberate white space to allow Example Figure 10.1 to be shown on a single page>

Comment [A286]: Clarification of relevant terminology is included in this paragraph.

Comment [A287]: EMA pre-authorisation procedural advice for users of the centralised procedure. 31 Mar 2016 EMA/339324/2007: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf
See 32. How are initial MAAs validated at the EMA: 'How to avoid most common GCP validation issues'. Information to be included in Appendix 16.1.4:
Please make sure that a table with the number of patients enrolled per country is included. These should be identified in the CSR of each study, for instance in Section 10.1 or Appendix 16.1.4.
Consider for PPD impact: CORE Reference suggests placement of this information in Appendix 16.1.4 and not in the main CSR text Section 10.1 to simplify redaction in the 'secondary use CSR' for public disclosure.
Disregard for studies outside the EU.

Comment [A288]: ICH E3 examples are: '(lost to follow-up, adverse event, poor compliance etc.)'.

Comment [A289]: Post-withdrawal contact with a subject may be protocol-defined.

Comment [A290]: Clarification to make a distinction between withdrawal of treatment and withdrawal from study. Footnote has been added in Example Figure 10.1 to clarify this further.

Comment [A291]: Clarification that table presentation, which is often used in practice, may alternatively be used.

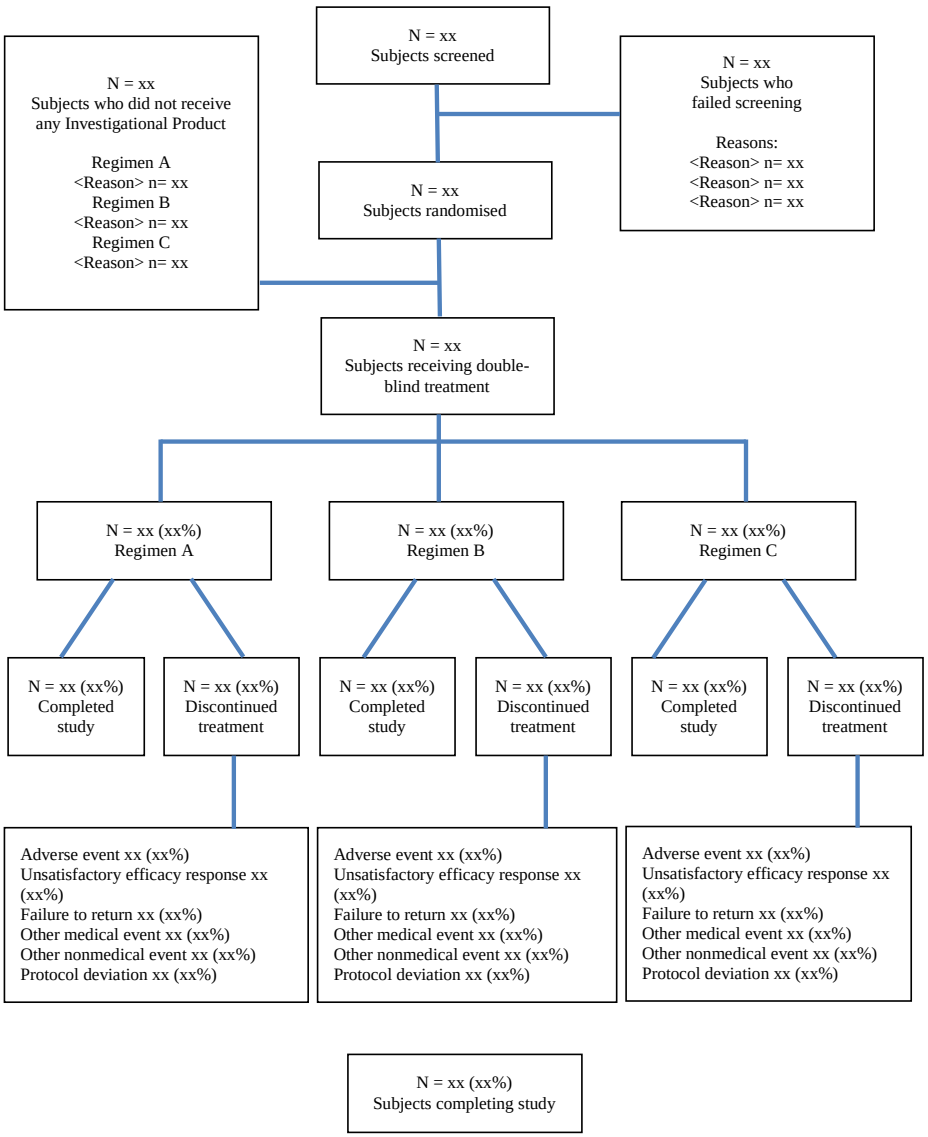
Comment [A292]: ICH E3 Annex IVa and IVb have been adapted to create Example Figure 10.1, which is included below.

Comment [A293]: ICH E3 Annex V Listing of Patients who Discontinued Treatment is cited in the ICH E3 text, but the text describes this incorrectly as 'patients discontinued from the study' when it actually means 'patients who discontinued treatment'. This is corrected here and, due to the distinction made between withdrawals and discontinuations above, it is suggested to also include a listing of withdrawn subjects, i.e. a listing should be prepared for both categories – subjects withdrawn from the study AND subjects who discontinued Investigational Product.

Annex V is renumbered as Annex II in CORE Reference.

Comment [A294]: ICH E3 Annex V is renumbered as Annex II in CORE Reference.

Example Figure 10.1. Disposition of Subjects in Protocol xxx



Footnotes:
Percentages are based on number of subjects receiving double-blind treatment.
'Discontinued' applies to subjects who stopped treatment. In some cases it may be appropriate to add another row for subjects withdrawn from the study. 'Withdrawn' applies to subjects who stopped treatment and who stopped all protocol-defined procedures.

(Data Source: xxx)

ICH E3 text *ICH E3 2012 Q&A text* CORE Reference text [Right margin comment=RATIONALE]

Comment [A295]: A flow chart is useful but is often not included in the CSR. The reason that this may be overlooked is because the ICH E3 example flowchart Annex IVa is not in the body of the ICH E3 document – inclusion of a flowchart is encouraged and ICH E3 Annex IVa and IVb have been adapted to create Example Figure 10.1, which is included in text.

This is a largely similar diagram (with enhancements to indicate disposition before subjects reach the point at which they receive double-blind medication) to the example flowchart in ICH E3 2012 Q & A 'Example Flowchart, Disposition of Patients': http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf.

Comment [A296]: Suggest to include protocol number in figure title to aid regulatory reviewers who often copy and paste key CSR information into their own summary documents.

Comment [A297]: Include the source of the data per the numbering of the data in the statistical output e.g. Section 14, Table 10.1.1.

10.2 PROTOCOL DEVIATIONS

All important deviations related to study inclusion or exclusion criteria, conduct of the study, subject management or subject assessment should be described. In Appendix 16.2.2, individual subjects with these observations should be listed, broken down by centre for multicentre studies. An example of such a listing is provided in Annex III.

In the body of the text, important protocol deviations should be appropriately summarised by centre and grouped into different categories, such as:

- Subjects who were enrolled (as determined by the protocol) in the study even though they did not satisfy the entry criteria
- Subjects who developed discontinuation or withdrawal criteria during the study but were not discontinued or withdrawn
- Subjects who received the wrong treatment or incorrect dose
- Subjects who received an excluded concomitant treatment.

Those protocol deviations that are not considered important can be referenced in the end of text listing.

<Deliberate wider line spacing below to allow optimal view of ICH E3 2012 Q&A text>

Definitions:

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Important protocol deviations (sometimes referred to as protocol violations or major protocol deviations) *are a subset of protocol deviations,* where a change, divergence or departure from the study requirements, whether by the subject or Investigator, resulted in a subject's withdrawal from study participation, or were regarded as severe enough to result in a subject's exclusion from one or more analysis sets (for example, per-protocol).

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Comment [A298]: ICH E3 Annex VI (Listing of Subjects and Observations Excluded from Efficacy Analysis), although mentioned, is not accurately described in text – clarification provided to reference the ICH E3 Annex VI end text listing. In addition, its number is changed from Annex VI to Annex III in CORE Reference.

Comment [A299]: Consider for PPD impact: By-centre grouping in the 'primary use CSR' enables data integrity to be assessed. However, by-centre grouping in the CSR text could compromise subject anonymity, particularly at low-recruiting centres. Consider data presentations that achieve anonymity in the 'secondary use CSR' for public disclosure.

Comment [A300]: ICH E3 uses 'entered'. Adapted to 'enrolled' to align terminology with that used in the CDISC Glossary and CORE Reference. The criteria for enrollment are typically defined by the protocol.

Comment [A301]: Clarification added on how to address those protocol deviations that are not considered important.

Comment [A302]: See ICH E3 2012 Q & A guidance text Point 7 for protocol deviations: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf
Added ICH E3 Q & A 2012 definitions of protocol deviations and important protocol deviations. There is no Japanese character for 'violation'; Japanese language uses the same character for 'violation' as for 'deviation'. This is why the term 'violation' is avoided by ICH.

Comment [A303]: From Annex IVa Subject Disposition of ICH E3 guidance – and as referenced in ICH E3 2012 Q & A, which explains that this was the intended meaning of 'protocol violation' in ICH E3.

Comment [A304]: In some studies, important protocol deviations may not be identified until the analysis phase when it is too late to withdraw the subject – rather, they would be excluded from one or more analysis sets.
This means that the ICH E3 text, reiterated in ICH E3 2012 Q & A text that states '…resulted in a subject's withdrawal from the study' is incomplete, and is therefore clarified here to account for late identification of protocol deviation, and the exclusion of such subjects from the relevant analysis population(s).
Examples to show why '…resulted in a subject's withdrawal from study participation' also holds true: Some clinical pharmacology studies do not exclude subjects from analysis populations unless a subject did not receive study drug. In efficacy studies, analyses may not always be done on subsets (per protocol analyses may not always be performed, even in Phase 2 and 3 studies).

As *the word 'violation' may have other meanings in a regulatory context, use of the term 'important protocol deviations' is encouraged; use of the term 'protocol violations' is discouraged. Sponsors may also choose to use another descriptor, provided that that the information presented is generally consistent with the definition of '*important protocol deviation*' provided above. Important protocol deviations may impact the completeness, accuracy and/or reliability of the study data or may affect a subject's rights, safety or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.*

The definition of important protocol deviations for a particular trial is determined in part by study design, the critical procedures, study data, subject protections described in the protocol, and the planned analyses of study data. In keeping with the flexibility of the ICH E3 *Guideline, Sponsors may amend or add to the examples of important deviations provided in E3 in consideration of a trial's requirements. Substantial additions or changes should be clearly described for the reviewer.*

10.3 DATA SETS ANALYSED

It is assumed that all subjects who received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

Exactly which subjects were included in each analysis set should be precisely defined, e.g. all subjects receiving any Investigational Products, all subjects with any efficacy observation or with a certain minimum number of observations, only subjects completing the study, all subjects with an observation during a particular time window, only subjects with a specified degree of compliance, etc. It should be clear, if not defined in the study protocol, when (relative to study unblinding), and how inclusion/exclusion criteria for the data sets analysed were developed, to ensure that a proper accounting of all subjects included in the analysis populations takes place. The procedure and criteria for allocation of subjects to a particular dataset (or exclusion from a dataset) should be specified in the SAP. Inclusion or exclusion of subjects into a particular dataset should be determined before database lock and documented in the TMF. Generally, even if the Sponsor's proposed primary analysis is based on a reduced subset of the subjects with data, there should also be, for any study intended to establish efficacy, an additional analysis using all randomised (or otherwise entered) subjects with any on-treatment data (i.e. an intention-to-treat analysis). For each analysis set, it should be clearly specified whether it was analysed "as assigned" or "as treated". A summary table of the subject evaluation groups/analysis populations should be presented in the CSR text.

There should be a listing of all subjects, visits and observations excluded from the defined analysis provided in Appendix 16.2 (see Annex III). The reasons for exclusions should also be analysed for the whole treatment group over time. Such a summary of exclusions from analysis populations is provided in Example Table 10.1.

Comment [A305]: Note: the term 'protocol violation' is common in device trials.

Comment [A306]: The direction to not use the term 'protocol violations' is not aligned with CDISC since the ICH E3 2012 Q & A takes precedence here over CDISC.

Comment [A307]: ICH E3 Section 11.1 (Data Sets Analysed) is relocated here. This is suggested because this section describes the subject population and is not part of the Efficacy Evaluation.

Comment [A308]: Clarification of ICH E3 text which states 'all patients entered into treatment who received'. 'Entered into treatment' is duplicative and is removed.

Comment [A309]: ICH E3 Section 12.1 (Extent of Exposure) final paragraph is more appropriately placed in CORE Reference Section 10.3 (Data Sets Analysed) so is relocated here. A cross-reference may be added in (CORE Reference) Section 10.6 (Extent of Exposure) to here if this adds clarity to the accounting of safety analysis subjects.

Comment [A310]: ICH E3 does not include any text around the fact that decisions about inclusion/exclusion of subjects from a dataset should be made before database lock and the decisions documented – instructional text has been adapted to include this.

Comment [A311]: From ICH E3, it is not clear how subjects who received the wrong treatment are handled so clarification is added about this.

Comment [A312]: ICH E3 does not explicitly state that subject evaluation groups/analysis populations should be summarised in a table and presented in text – suggest this should be presented.

Comment [A313]: The ICH E3 word 'tabular' is omitted as considered redundant.

Comment [A314]: ICH E3 states: '…in appendix 16.2.3 (see Annex VI of the guideline for an example)'. The reference to the appendix and annex are modified.

Comment [A315]: ICH E3 Annex VII relocated in text (as Example Table 10.1). It is not referenced within the ICH E3 results text.

Example Table 10.1. Exclusions From Analysis Sets in Protocol xxx

Reason Category	Treatment Group N=x	Time point 1 n excluded	Time point 2 n excluded	Time point x n excluded
TOTAL				

Data source: xxx

10.4 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Group data for the critical demographic and baseline characteristics of the subjects, as well as other factors arising during the study that could affect response, should be presented in this section and comparability of the treatment groups for all relevant characteristics should be displayed by use of tables or graphs in Section 14.1 (Demographic Data). The data for the subject sample included in the "all subjects with data" analysis should be given first. This can then be followed by data on other groups used in principal analyses, such as the "per-protocol" analysis or other analyses, e.g. groups defined by compliance, concomitant disease/treatment, or demographic/baseline characteristics. When such groups are used, data for the complementary excluded group should also be shown. In a multicentre study, where appropriate, comparability should be assessed by centre or region, and centres or regions should be compared.

The critical variables will depend on the specific nature of the disease and on the protocol but will usually include:

- Demographic variables
  - age
  - sex
  - race
- Disease factors
  - specific entry criteria (if not uniform), duration, stage, severity of disease and other clinical classifications and sub-groupings in common usage or of known prognostic value
  - baseline values for critical clinical measurements carried out during the study or identified as important indicators of prognosis or response to therapy
  - concomitant illness at study initiation, such as renal disease, diabetes, heart failure
  - relevant previous illness
  - relevant previous treatment for illness treated in the study
  - concomitant treatment maintained even if the dose was changed during the study, including oral contraceptive and hormone replacement treatment; treatments stopped at entry into the study period (or changed at study initiation); and concomitant treatments started during the study period. Treatment group differences, and trends with increasing dose, should be noted, if applicable. Note: prior medications are those that start and finish prior to first administration of Investigational Product. Concomitant medications are those that start prior to first administration of Investigational Product and finish or are ongoing on or after first

Comment [A316]: Suggest to include protocol number in figure title to aid regulatory reviewers who often copy and paste key CSR information into their own summary documents.

Comment [A317]: Consider for PPD impact: Although the data in example Table 10.1 will be aggregated, de-anonymisation of individual subjects may be possible where small numbers of subjects present with a particular reason for exclusion. Therefore, data in example Table 10.1 may need redaction in the 'secondary use CSR' for public disclosure.

Comment [A318]: Include the source of the data per the numbering of the data in the statistical output.

Comment [A319]: See ICH E3 Q & A 2012: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Q_As_Step4.pdf Point 1 which states: '*...consider demographic baseline information. E3 suggests presentation of this information in the efficacy evaluation, but many variations of this presentation are possible. For example, if the efficacy and safety populations differ substantially, it would be appropriate to present demographic and baseline characteristics for the safety and efficacy populations in the safety and efficacy sections or in a new section preceding the efficacy and safety results sections*'.

ICH E3 Section 11.2 (Demographic and Other Baseline Characteristics) content is presented in 'new' Section 10.4.
Demography, medical history, prior medications etc. relate to the safety as well as the efficacy population.

Comment [A320]: Clarification from Health Canada on rationale behind this particular piece of ICH E3 text and why it needs to remain 'in situ' is as follows: 'It is important to show or explain clearly why certain groups / data are excluded from the analyses. The data / groups that are left out of the per-protocol analyses need to be justified. At times, this may require showing the data from the excluded groups'.

Comment [A321]: 'or regions' added to allow for region comparisons, as applicable.

Comment [A322]: ICH E3 text 'A diagram showing the relationship between the entire sample and any other analysis groups should be provided' has been omitted as data should ideally be summarised in Section 10.1 (Disposition of Subjects) which shows the flow of subjects through the study.

administration of Investigational Product, or those that start on or after first administration of Investigational Product but no later than the last dose of Investigational Product. Medications that start after the last dose of Investigational Product are considered post-treatment. A window may be defined after last dose of Investigational Product where a medication may still be considered concomitant. The length of the window defined should be study-specific

- Other factors that might affect response to therapy (e.g. weight, renin status, antibody levels, metabolic status)
- Other possibly relevant variables (e.g. smoking, alcohol intake, special diets) and, for women, menstrual status and date of last menstrual period, if pertinent for the study.

In addition to tables or graphs giving group data for these baseline variables, relevant individual subject demographic and baseline data, including laboratory values, and all concomitant medication for all individual subjects randomised (broken down by treatment and by centre for multicentre studies) should be presented in by-subject listings in Appendix 16.2.4. Although some regulatory authorities will require all baseline data to be presented elsewhere in listings, the appendix to the study report should be limited to only the most relevant data, generally the variables listed above.

This content may be sub-sectioned, for example:

10.4.1 Demography

10.4.2 Baseline Disease Characteristics

10.4.3 Medical History and Concurrent Illnesses

10.4.4 Prior and Concomitant Treatments

10.5 MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment compliance describes the degree to which a subject takes their intended full dose of Investigational Product and may be expressed as a percentage. Extent of treatment exposure describes the cumulative dose amount received by the subject and should be included, for example, in Section 10.6 (Extent of Exposure).

If any randomised subjects were excluded from analysis due to non- / poor compliance to treatment it should be explained.

Any measurements of compliance of individual subjects with the treatment regimen under study and drug concentrations in body fluids should be summarised, analysed by treatment group and time interval and tabulated in Appendix 16.2.5.

10.6 EXTENT OF EXPOSURE

Analysis of safety- and efficacy-related data should take into account the extent of exposure (dose, duration, number of subjects) to determine the degree to which safety and efficacy can be assessed from the study.

Comment [A323]: Concomitant medications are not clearly specified in ICH E3, nor is a distinction made between prior and concomitant (on study) medications. Suggest to include prior and concomitant medications. Clarification is added to include definitions.

Comment [A324]: The ICH E3 word 'tabular' is omitted as considered redundant.

Comment [A325]: Example sub-sections are provided to minimise the possibility of data omissions.
If by-centre or by-region presentations are available, these may be equally well presented either in, for example, Section 10.4 or in Section 11.2.4 Multicentre studies, with appropriate cross-referencing.

Comment [A326]: ICH E3 Section 11.3 (Measurements of Treatment Compliance) content is presented in 'new' Section 10.5, as treatment compliance relates to all study subjects, not just those with efficacy data.

Comment [A327]: Clarification to include the definitions of 'compliance' and 'exposure' to avoid any misplacement of exposure data in this section.

Comment [A328]: It is suggested to mention this and cross-referenced to the detailed presentation in, for example, Section 10.3 (Data Sets Analysed).

Comment [A329]: ICH E3 Section 12.1 (Extent of Exposure) content is presented in 'new' Section 10.6, as extent of exposure relates to all study subjects, not just those with safety data.

Comment [A330]: ICH E3 text relocated from Section 12. Safety Evaluation, because extent of exposure affects both efficacy and safety.

The extent of exposure to the Investigational Product(s) should be characterised according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed.

- Duration: Duration of exposure to any dose can be expressed as a median or mean, but it is also helpful to describe the number of subjects exposed for specified periods of time, such as for one day or less, two days to one week, more than one week to one month, more than one month to six months, etc. The numbers exposed to Test Product(s) for the various durations should also be broken down into age, sex, and racial subgroups, and any other pertinent subgroups, such as disease (if more than one is represented), disease severity, concurrent illness

- Dose: The mean or median dose used and the number of subjects exposed to specified daily dose levels should be given; the daily dose levels used could be the maximum dose for each subject, the dose with longest exposure for each subject or the mean daily dose. It is often useful to provide combined dose-duration information, such as the numbers exposed for a given duration (e.g. at least one month) to the most common dose, the highest dose, the maximum recommended dose, etc. In some cases, cumulative dose might be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/m^2 basis, as appropriate. The numbers of subjects exposed to various doses should be broken down into age, sex and racial subgroups, and any other pertinent sub-groups.

It is assumed that all subjects who received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

Subject exposure to Investigational Product also impacts the assessment of efficacy. Definition of exposed subjects evaluable for efficacy is study-dependent. Details should be provided.

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Comment [A331]: See Section 10.5 (Measurements of Treatment Compliance) for definition of 'extent of exposure' which is placed alongside the definition of 'treatment compliance' so the two definitions are more easily shown to be distinct from one another.

Comment [A332]: ICH E3 states 'The extent of exposure to test drugs/investigational products (and to active control and placebo)…' Terminology is clarified here to 'Investigational Product(s)'.

Comment [A333]: ICH E3 states 'test drug/investigational product'. Language is clarified as meaning 'Test Product'. See Preface for terminology used for the Investigational Product.

Comment [A334]: ICH E3 text from Section 12.1 (Extent of Exposure) 'If available, drug concentration data (e.g. concentration at the time of an event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events or changes in laboratory variables. (Appendix 16.2.5.)' has been relocated to Section 11.3 (PK, PD and Other Analyses).

Extent of exposure refers to cumulative dose amount rather than measured drug concentration, hence, removal of any reference to drug concentration data in this section is considered valid.

Comment [A335]: ICH E3 text states 'entered into treatment'. Text is duplicative and not necessary and is therefore omitted.

Comment [A336]: It is suggested to mention this and cross-reference to the detailed presentation in, for example, Section 10.3 (Data Sets Analysed).

Comment [A337]: Clarification that exposure impacts efficacy and that definition of efficacy-evaluable subjects is study-dependent.

Comment [A338]: It is suggested to mention this and cross-reference to the detailed presentation in, for example, Section 10.3 (Data Sets Analysed).

11. EFFICACY AND OTHER EVALUATIONS

The example section headings should be adapted to reflect study design.

11.1 EFFICACY RESULTS

Treatment groups should be compared for all measures of efficacy described in the protocol (primary, secondary, and other [including exploratory endpoints]) and the results presented. The results of analysis of drug concentration (PK) and PD (including biomarkers) endpoints should be presented (for example in Section 11.3 [Pharmacokinetic, Pharmacodynamic and Other Analyses Results]).

If a planned analysis is to be conducted at a later date so that results are not included in this CSR (e.g. a follow-up for survival after one year), this should be stated.

In general, the results of all analyses contemplated in the protocol and an analysis including all subjects with on-study data should be performed in studies intended to establish efficacy. The analysis should show the size (point estimate) of the difference between the treatments, the associated confidence interval and, where utilised, the results of hypothesis testing.

If an active control study is intended to show equivalence (i.e. a difference not exceeding a specified size) between the Test Product and the active comparator (control), the analysis should show the confidence interval for the comparison between the two agents for critical endpoints and the relation of that interval to the prespecified degree of inferiority that would be considered unacceptable. (See, for example, Section 9.2 [Discussion of Study Design, Including the Choice of Control Groups] for important considerations when using the active control equivalence design.)

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Comment [A339]: See **Clarification on general approach to report structuring** note in Section 9.5. Note that the title (Efficacy and Other Evaluations) can be changed if necessary, e.g. for a study in which PK is a primary endpoint.

Comment [A340]: ICH E3 Section 11.1 (Data Sets Analysed) relocated to Section 10.3 because the Data Sets Analysed content describes the subject population and is not exclusively part of the Efficacy Evaluation.

Comment [A341]: ICH E3 '…and Tabulations of Individual Patient Data" is omitted from the end of this title.

Comment [A342]: ICH E3 'benefit/risk assessment' text has been relocated from here to Section 13 (Discussion and Overall Conclusions) as it was deemed more relevant to place this text in the conclusion section.

Comment [A343]: ICH E3 instructional text states only: '(primary and secondary end-points; pharmacodynamic endpoints studied)' and therefore may not cover all potential analyses or make it clear that the analyses produced should relate to the endpoints stated and analyses planned in the protocol. Clarification is added to cover primary, secondary and other (including exploratory) analyses of efficacy and to specify where results from each of these should be presented, incl PK/PD analyses.

Comment [A344]: ICH E3 mentions PD endpoints. Suggest these are better placed in Section 11.3.

Comment [A345]: ICH E3 instructional text does not cover how to handle planned analyses not yet performed at time of reporting – clarification added.

Comment [A346]: ICH E3 text: '(i.e. lack of a difference greater than a specified size)' is clarified.

Comment [A347]: ICH E3 states '…between the test drug/investigational product and the active control/comparator'. The language is clarified here. See preface for terminology for Investigational Product.

Comment [A348]: ICH E3 Section 11.4.2.7 (Active-Control Studies Intended to Show Equivalence) text relocated here with minor modifications, as non-inferiority studies would have primary analysis designed to test this hypothesis with results presented in Section 11.1 rather than ICH E3 Section 11.4.2.7.

The endpoints defined for the study may consist of continuous variables (e.g. mean blood pressure or depression scale score), categorical responses (e.g. cure of an infection), or survival data (time-to-progression in an oncology study) amongst others. Results may need to be presented from different analyses in order to address the primary and secondary objectives of the study. Results from analysis of related variables or additional timepoints may be presented to support the primary and secondary analyses. For example even if one variable receives primary attention (e.g. in a blood pressure study, supine blood pressure at Week x), other reasonable measures (e.g. standing blood pressure and blood pressures at other particular times) should be assessed, at least briefly. In addition, the time course of response should be described, if possible.

If any critical measurements or assessments of efficacy or safety outcomes were made by more than one party (e.g. both the Investigator and an expert committee may offer an opinion on whether a subject had an acute infarction), overall differences between the ratings should be shown and each subject having disparate assessments should be identified, without compromising subject identity. The data for these individual subjects with disparate assessments must not be displayed by centre, nor must verbatim text be reproduced in the CSR text. The assessments used should be clear in all analyses.

In many cases, efficacy and safety endpoints are difficult to distinguish (e.g. deaths in a fatal disease study). Many of the principles addressed below should be adopted for critical safety measures as well.

Any analyses not specified in the protocol or SAP (i.e. *post-hoc* analyses) must be distinguished from pre-planned analyses, for example, in Section 11 (Efficacy and Other Evaluations), or these may be included in Appendix 16.1.9. Further guidance on Appendix 16.1.9 may also be found in Annex IV.

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Comment [A349]: ICH E3 text 'Analyses based on…' is clarified as meaning 'The endpoints defined for the study may consist of…'

Comment [A350]: Added 'survival data' to show variables are not limited to continuous and categorical.

Comment [A351]: Rewording emphasises that CSR may need to present results from different types of analyses to address all protocol objectives.

Comment [A352]: ICH E3 instructional text 'For a multicentre study, where appropriate, data display … especially the larger sites' has been omitted as this is covered in Section 11.2.4 (ICH E3 Section 11.4.2.4 Multicentre Studies).

Comment [A353]: Consider for PPD impact: Subject numbers may be created using a centre identifier component. Subject re-identification, particularly for centres entering small numbers of study subjects, may be possible through a subject number that includes a centre identifier component. Where individual subject numbers are presented in the 'primary use CSR', it is recommended that these are fully redacted in the 'secondary use CSR' for public disclosure. In all cases, the entire subject number – including any centre identifier component – should be redacted.

No grouping by centre in the 'primary use CSR' will minimise the need for text modification in the 'secondary use CSR'.

Comment [A354]: Consider for PPD impact: Investigator verbatim text may include clues to the identitity of the subject. If relevant verbatim text is paraphrased in 'primary use CSR' this will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A355]: ICH E3 does not mention possible *post-hoc* efficacy analyses. Clarification is added to ensure reporting of *post-hoc* analyses - in the main CSR or Appendix 16.1.9, as the Sponsor deems appropriate – is not overlooked.
In some cases, it may be preferable to fully integrate *post-hoc* results and conclusions, (e.g. if a better sequencing or genotyping method becomes available after database lock, and *post-hoc* analyses use this new method to more precisely define subject subgroups) so that *post-hoc* data are located within the appropriate results section. There must be clear identification that these are *post-hoc* data. It should be noted that with such an integrated results presentation, there is risk of losing the distinction that some of those results (*post-hoc*) are subject to a greater degree of bias than those results for pre-planned analyses - because they were performed post-unblinding.

The presentation of results may be split into example sub-sections, the inclusion and order of which should reflect the design of the individual study:

11.1.1 Primary Efficacy Endpoint

11.1.2 Secondary Efficacy Endpoints

11.1.3 Other Efficacy Endpoints

If applicable. Include exploratory efficacy endpoints.

11.1.4 *Post-hoc* Analyses

If applicable, and if not integral to, for example, Sections 11.1.1-11.1.3.

11.2 RESULTS OF STATISTICAL ISSUES ENCOUNTERED DURING THE ANALYSIS

The statistical analysis used should be described for clinical and statistical reviewers in the text of the report, with detailed documentation of statistical methods (see Annex IV) presented in Appendix 16.1.9 and outlined in, for example, Section 9.5 (Efficacy and Safety Variables). Important features of the analysis including adjustments made for demographic or baseline measurements or concomitant therapy; handling of withdrawals, discontinuations and missing data; adjustments for interim analyses; special analyses of multicentre studies; and adjustments for multiple comparisons should be discussed. Any changes in the analysis made after unblinding should be identified. In addition to the general discussion, the afore-mentioned specific issues should be addressed (unless not applicable) including the results of any analyses performed to address those specific statistical issues. If no such issues arose during the study, then a statement can be added to the effect of 'No statistical issues arose during the analysis of the study data'.

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Comment [A356]: Suggested example sub-sections may help structure the CSR.

Comment [A357]: ICH E3 Section 11.2 (Demographic and Other Baseline Characteristic) relocated to Section 10.4 because demography, medical history, prior medications etc. relate to the safety as well as the efficacy population.

Comment [A358]: Suggest amending ICH E3 section title to remove 'analytical' which usually refers to PK. PK is now covered in Section 11.3. This also clarifies that the statistical issues referred to are those encountered during the statistical analysis, and that it is the results (not the methods) of these issues that are presented.

Comment [A359]: ICH E3 Annex IX (but this was misnumbered in ICH E3 and should have been Annex VIII). It is Annex IV in CORE Reference.

Comment [A360]: Methodologies for the 'statistical issues' are relocated to Section 9.5 – to more logically separate the methodologies for the statistical issues from the results of those statistical issues.

Comment [A361]: ICH E3 reference to 'particular methods used' is omitted, as these are relocated to Section 9.5.

Comment [A362]: Clarification of terminology for consistent use of withdrawal and discontinuation, because in practice, the term used in ICH E3 i.e. 'dropout', is often used in relation to the sample size calculation (dropout rate).

Comment [A363]: The order of the 'issues' are matched with the order of the suggested sub-sections below.

Comment [A364]: ICH E3 text is 'blind-breaking'. Clarified as 'unblinding'.

Comment [A365]: Suggest in this case that the subsequent example sub-sections may be omitted.

11.2.1 Adjustments for Covariates

The results of analyses investigating the impact of covariates should be discussed here with supportive information (e.g. analysis of covariance [ANCOVA] or Cox regression output) included in the detailed documentation of statistical methods in Appendix 16.1.9. If the covariates or methods used in these analyses differed from those planned in the SAP, the differences should be explained and the results presented.

11.2.2 Handling of Withdrawals, Discontinuations or Missing Data

There are several factors that may affect withdrawal and/or discontinuation rates. These include the duration of the study, the nature of the disease, the efficacy and toxicity of the drug under study and other factors that are not treatment related. Ignoring the subjects who withdrew or discontinued and drawing conclusions based only on subjects who completed the study can be misleading. A large number of withdrawn or discontinued subjects, however, even if included in an analysis, may introduce bias, particularly if there are more early withdrawn or discontinued subjects in one treatment group or the reasons for withdrawal or discontinuation are treatment- or outcome-related. Although the effects of early withdrawal or discontinuation, and sometimes even the direction of bias, can be difficult to determine, possible effects should be explored as fully as possible. Analyses may be repeated for the population of randomised subjects with any on-study measurements and for the population of completing subjects to see if the results observed for the completing subjects reflect those seen in the primary analysis population. The results of any such repeat analyses should be presented.

11.2.3 Interim Analyses and Data Monitoring

A summary of the results from any interim analyses or a cross-reference to the results (e.g. an interim study report) should be included.

11.2.4 Multicentre Studies

If appropriate, demographic, baseline and post-baseline data, as well as efficacy data, may be presented by centre, even though the combined analysis is the primary one. The effect of centre, the significance of the interaction term and any extreme or opposite results among centres should be noted and discussed, considering such possibilities as differences in study conduct, subject characteristics or clinical settings. The centres should have sufficient numbers of subjects to make such analysis feasible.

Comment [A366]: ICH E3 Section 11.4.2.1 text states: '… results of analyses, and supportive information (e.g., ANCOVA or Cox regression output) should be included in the detailed documentation of statistical methods.' This is clarified.

Comment [A367]: If the difference was a change in methodology it should already have been documented in, for example, Section 9.8, and this may be cross-referenced.

Comment [A368]: ICH E3 text omitted as it is not relevant to the CSR: 'Although not part of the individual study report, comparisons of covariate adjustments and prognostic factors across individual studies may be an informative analysis in a summary of clinical efficacy data'.

Comment [A369]: Clarification of terminology in this title and paragraph below for consistent use of 'withdrew/discontinued' and 'withdrawn or discontinued subjects', because in practice, the term used in ICH E3 i.e. 'drop out', is often used in relation to the sample size calculation (dropout rate).

Comment [A370]: ICH E3 text 'It may be helpful to examine the observed cases at various time points or, if dropouts were very frequent, to concentrate on analyses at time points when most of the patients were still under observation and when the full effect of the drug was realised. It may also be helpful to examine modelling approaches to the evaluation of such incomplete data sets' is consolidated here to cover two alternatives – either using a completers population or using an imputation method to account for missing data.

Comment [A371]: ICH E3 Section 11.4.2.3 text on (Interim Analyses and Data Monitoring) is wholly relocated to Section 9.7.1 since the text relates wholly to methodology and not to results. A reminder is added to report the results of any such analysis in this section.

Comment [A372]: Definition of multicentre study is relocated to Section 9.7.1 as this is methodological text.

Comment [A373]: This CORE Reference text is a consolidation and clarification of the ICH E3 Section 11.4.2.4 text 'Individual centre results should be presented…centre differences with respect to response'.

Comment [A374]: Consider for PPD impact: By-centre grouping of results in the text of the CSR will require particular consideration as could compromise subject anonymity. Be aware that redaction of 'primary use CSR' text (for regulatory submission) in the 'secondary use CSR' (for public disclosure) may be necessary.

11.2.5 Multiple Comparison/Multiplicity

If adjustments for multiple comparisons/multiplicity have been made, the results of the analyses may have already been presented as part of the results for primary, and secondary if applicable, endpoints. If not already presented elsewhere then results arising out of multiple testing may be presented here.

11.2.6 Use of an "Efficacy Subset" of Subjects

Particular attention should be devoted to the effects of excluding subjects with available data from analyses because of poor compliance, missed visits, ineligibility, or any other reason considered to constitute an important protocol deviation, and the results presented. An analysis using all available data should be carried out for all studies intended to establish efficacy, and the results presented. In general, it is advantageous to demonstrate robustness of the principal study conclusions with respect to alternative choices of subject populations for analysis. Any substantial differences resulting from the choice of subject population for analysis should be explicitly discussed.

11.2.7 Examination of Subgroups

If the size of the study permits it, pre-defined subgroups based on important demographic or baseline data should be examined for unusually large or small responses and the results presented, e.g. comparison of effects by age group, sex, or race, by severity or prognostic groups, by history of prior treatment with a drug of the same class, etc. If these analyses were not carried out because the study was too small it should be noted. These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, subject selection, dose selection, etc. Where there is a prior hypothesis of a treatment effect in a particular subgroup, this hypothesis and its assessment should be part of the planned statistical analysis reported, for example, in Section 9.7 (Statistical Methods Planned in the Protocol and Determination of Sample Size).

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Comment [A375]: ICH E3 Section 11.4.2.5 text on (Multiple Comparisons/Multiplicity) is wholly relocated to Section 9.7.1 since the text relates wholly to methodology and not to results.
A reminder is added to report the results of any such analysis with multiple comparison/multiplicity content, if not elsewhere.

Comment [A376]: Clarification of ICH E3 term 'dropping patients'.

Comment [A377]: See Section 10.2 (Protocol Deviations) for definition of 'important protocol deviation'.

Comment [A378]: If this efficacy subset (or "Per-Protocol Population") is the population defined as the analysis of the primary endpoint, then text may be, for example, in Section 11.1.1 (Primary Efficacy Endpoint), in which case, a cross-reference may be helpful. Otherwise, suggest presenting the results here.

Comment [A379]: Results may be in Section 11.1 [Efficacy Results] if this is already defined as a primary or secondary endpoint), in which case, a cross-reference may be helpful. Otherwise, suggest presenting the results here.

Comment [A380]: Clarification of ICH E3 text: '… should be the subject of explicit discussion'.

Comment [A381]: ICH E3 Section 11.4.2.7 (Active-Control Studies Intended to Show Equivalence) text is relocated (with minor modifications) to Section 11.1, as non-inferiority studies would have primary analysis designed to test this hypothesis with results presented in Section 11.1 rather than here.

Comment [A382]: Suggest that a requirement for subgroups to be pre-defined is necessary.

Comment [A383]: 'group' added to ICH E3 text as subgroups must based on categorical variables, of which 'age' itself is not one.

Comment [A384]: 'treatment' replaces ICH E3 term 'differential' which lacks clarity.

Comment [A385]: If the results have already been presented in Section 11.1 (Efficacy Results), suggest these may be cross-referenced.

11.2.8 Tabulation of Individual Response Data

In addition to tables and graphs representing group data, individual response data and other relevant study information should be presented in tables.

If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

Include only a cross-reference to Appendix 16.2.6 that presents the individual efficacy response data.

11.3 PHARMACOKINETIC, PHARMACODYNAMIC AND OTHER ANALYSES RESULTS

Pharmacokinetic and PD (including biomarkers) data, etc. may be included using the following (or adapted) example subheadings.

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Comment [A386]: The text in this section from ICH E3 Section 11.4.3 relates to creation of listings and is primarily used by statisticians. It does not appear in any other guidance document than ICH E3. Clarification is given that only a cross-reference is required to the relevant data in the text of the CSR.
The actual relevant ICH E3 Section 11.4.3 (Tabulation of Individual Response Data) text and for ICH E3 Section 11.4.6 (By-patient displays) is relocated to Annex IV.

Comment [A387]: Consider for PPD impact: For studies that examine small subpopulations using genetic markers, particularly at a centre level, it will be virtually impossible to prevent subject de-identification. Caution is advised to avoid de-identification, particularly in such cases. See also March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 36 of 91, which states: 'Clinical trials conducted on rare diseases and on small populations may have a high risk of re-identification. Therefore, specific attention should be given to these scenarios. …This approach is also applicable to genetic information and low frequency events (e.g. rare events, extreme values, unusual treatments, pregnancy outcomes).'

Comment [A388]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A389]: ICH E3 Section 11.3 (Measurements of Treatment Compliance) relocated to Section 10.5. Treatment compliance relates to all study subjects, not just those with efficacy data.

Comment [A390]: Section title is added to add clarity on where to report PK, PD and other data, remembering that if any of these represent the primary objective/endpoint of the study, adapt report structure accordingly: see **Clarification on general approach to report structuring** note in Section 9.5.

11.3.1 Drug Dose, Drug Concentration and Relationships to Response

Include reporting of the results of drug concentration (PK) data.

When the dosage in each subject can vary, the actual doses received by subjects should be shown and individual subject's doses should be tabulated. Although studies not designed as dose-response studies may have limited ability to contribute dose-response information, the available data should be examined for whatever information they can yield. In examining the dose response, it may be helpful to calculate dose as mg/kg body weight or mg/m^2 body surface.

Drug concentration information, if available, should also be tabulated (Appendix 16.2.5), analysed in PK terms and, if possible, related to response. If any PK data (e.g. concentration at the time of an event, C_{max}, AUC) is pertinent in individual subjects for correlation with AEs or changes in laboratory values (Appendix 16.2.5), this should be mentioned.

Further guidance on the design and analysis of studies exploring dose-response or concentration response can be found in the ICH Guideline "Dose-Response Information to Support Drug Registration" (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E4/Step4/E4_Guideline.pdf).

If any PK modelling has been undertaken, the top-line results should be included.

11.3.2 Drug-Drug and Drug-Disease Interactions

Any apparent relationship between response and concomitant therapy and between response and past and/or concurrent illness should be described.

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Comment [A391]: Introductory sentence for avoidance of doubt.

Comment [A392]: In studies where the drug concentration (PK) data is the primary endpoint, it may be more appropriate to present the data in, for example, Section 11.1 (Efficacy Results).

Comment [A393]: ICH E3 text relocated from Section 12.1 (Extent of Exposure) 'If available, drug concentration data (e.g. concentration at the time of an event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events or changes in laboratory variables (Appendix 16.2.5)' and reworded for clarity.

Comment [A394]: Addition of web address for ICH E4 guideline (1994) for transparency.

Comment [A395]: Clarification to indicate that the results of any PK modelling of the drug concentration-time data should be included here.

Comment [A396]: Suggest sub-headings may be useful to match the measurements, for example, as shown in Section 9.5.3 (PK and PD Measurements).

Comment [A397]: In studies where the drug-drug or drug-disease interaction is a primary or secondary endpoint, it may be more appropriate to present the data, for example in Section 11.1 Efficacy Results.

Comment [A398]: ICH E3 Section 11.4.6 (By-patient displays) is relocated to CORE Reference Annex IV.

11.3.3 Other Endpoints

Other study-specific endpoints (for example, PD [which may include biomarkers], pharmacogenomics, quality of life and pharmacoeconomic endpoints) may be described.

11.4 EFFICACY RESULTS SUMMARY

Include a bullet list summarising the main efficacy (and/or other relevant) results of the study, and without interpretation or drawing of conclusions.

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Comment [A399]: To allow inclusion of 'other endpoints' such as those listed

Comment [A400]: ICH E15 Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories Step 4, 1 Nov 2007 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E15/Step4/E15_Guideline.pdf.

Comment [A401]: Suggest to adapt the title to suit study design. For e.g. a study with no efficacy but with a PK component, the heading could be renamed 'Pharmacokinetic Results Summary'.

Comment [A402]: ICH E3 has Section 11.4.7 (Efficacy Conclusions). Suggest the inclusion of 'Efficacy Results Summary' and 'Safety Results Summary' sub-sections, directly after the respective main results sections. Note that these suggested sections do not include the word 'conclusions' and should not include any interpretation or conclusions but should merely (bullet) summarise the main results. Such summaries are useful for writing the Synopsis and other related sections (e.g. Discussion and Overall Conclusions).

It should be noted that these example sub-sections can be omitted if desired. The important point is NOT to have conclusions drawn in 2 separate places in the report.

12. SAFETY EVALUATION

Analysis of safety-related data can be considered at three levels. First, the extent of exposure (dose, duration, number of subjects) should be examined to determine the degree to which safety can be assessed from the study. Second, the more common AEs, laboratory test changes, etc. should be identified, classified in some reasonable way, compared for treatment groups and analysed, as appropriate, for factors that may affect the frequency of adverse reactions/events, such as time dependence, relation to demographic characteristics, relation to dose or drug concentration, etc. Finally, SAEs and other clinically meaningful AEs should be identified, usually by close examination of subjects who left the study prematurely because of an AE, whether or not identified as drug related, or who died.

The ICH E2A Guideline on Clinical Safety Data Management; Definitions and Standards for Expedited Reporting (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf) defines SAEs as follows: A "serious adverse event" (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

For the purpose of this guideline, "other clinically meaningful AEs" include marked haematological and other laboratory abnormalities plus any AEs that led to an intervention, including withdrawal of drug treatment, dose reduction or notable additional concomitant therapy.

In the following sections, three kinds of analysis and display are called for:
1) Summarised data, often using tables and graphical presentations presented in the main body of the report
2) Listings of individual subject data, and
3) Narrative statements of events of particular interest. Narratives may include verbatim Investigator text or text combinations that may contribute to de-anonymisation.

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Comment [A403]: See **Clarification on general approach to report structuring** note in Section 9.5.

Comment [A404]: Extent of exposure may also be relevant for analysis of efficacy-related data and is therefore more appropriately relocated to Section 10. (Study Subjects). Consider cross-referencing to content on 'Study Subjects'.

Comment [A405]: ICH E3 uses 'other significant AEs'. Suggest not to use the term 'significant' by itself. Use a descriptor before significant, e.g. statistically significant, clinically significant. Alternative phraseology could include 'clinically relevant' or 'clinically meaningful' – latter is used in CORE Reference. Explain any wording choices.

Comment [A406]: Clarification – 'other clinically meaningful AEs' includes discontinuations due to AEs and other AEs of special interest (which include marked haematological and other laboratory abnormalities and AEs leading to intervention, dose reduction or notable additional concomitant treatment) – as indicated in 3rd paragraph of this section (below).

Comment [A407]: ICH E3 uses 'other significant AEs'.

Comment [A408]: Consider for PPD impact: ICH E3 states that narratives may be placed in Section 12.3.2 (i.e. integral to the main CSR text; CORE Reference Section 12.2.2) or in Section 14.3.3 (i.e. in the end-of-text tables section, subordinate to the main CSR text). Suggest that placement in Section 14.3.3 could ease redaction in the 'secondary use CSR' for public disclosure in regions where the entire Section could be redacted.

Note that in the EU, March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) Chapter 2, Section 2.2 states that 'Case narratives should not be removed or redacted in full regardless of their location within the clinical reports (body of the report or listings). They should be instead anonymised'.

For narratives it is particularly important to consider data presentations that maintain data meaning, remain in context AND conform to current minimum standards for de-identifying data.

In regions where full narrative redaction is not allowed (i.e. EU), for studies with large numbers of narratives, the narratives should be placed in Section 14.3.3 so as not to interrupt the flow of CSR text.

If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

In all tabulations and analyses, events associated with Test Product and/or Control Product should be displayed.

All AEs for each subject, including the same event on several occasions, should be listed in Appendix 16.2.7, giving both preferred term and the original (verbatim) term used by the Investigator.

The listing should be by Investigator and by treatment group and should include:

- Subject identifier
- Age, race, sex, weight (height, if relevant)
- The AE (preferred term, verbatim term)
- Duration of the AE
- Severity (e.g. mild, moderate, severe)
- Seriousness (serious/non-serious)
- Action taken (e.g. none, dose reduced, treatment stopped, specific treatment instituted etc.)
- Outcome (e.g. Council for International Organisations of Medical Sciences [CIOMS] format)
- Causality assessment (e.g. related/not related). How this was determined should be described in the protocol
- Date of onset or date of clinic visit at which the event was discovered
- Timing of onset of the AE in relation to last dose of Investigational Product (when applicable)
- Duration of Investigational Product treatment
- Investigational Product at time of event or most recent Investigational Product taken
- Investigational Product dose in absolute amount, mg/kg or mg/m^2 at time of event.

Any abbreviations and codes should be clearly explained at the beginning of the listing or, preferably, on each page.

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Comment [A409]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A410]: Consider for PPD impact: Verbatim text in the listings should not be presented in the text of the 'primary use CSR' for regulatory review, as verbatim text may present the opportunity for de-anonymisation of individual subjects. This recommendation is to help avoid the need for piecemeal redaction of 'primary use CSR' text, in the 'secondary use CSR' for public disclosure.

Comment [A411]: ICH E3 Section 12.2.4 (Listing of AEs by patient).

Comment [A412]: Some of the items included in the ICH E3 list (in ICH E3 Section 12.2.4) are never actually included in the AE listing (although the data may be provided elsewhere). For example:
- Location of CRFs, if provided
- Drug concentration (if known)
- Concomitant treatment on study

These items have been omitted from the bullet list.

Comment [A413]: ICH E3 uses 'reported'. This term is clarified as 'verbatim'.

Comment [A414]: Equivalent in US is MedWatch.

Comment [A415]: ICH E3 text states 'described in the table or elsewhere'. Clarification is added to explain that the description should appear in the protocol.

Comment [A416]: Clarification of ICH E3 wording 'test drug/investigational product' as meaning Investigational Product in the last 4 bullets in this list. See Preface for terminology related to Investigational Product.

Comment [A417]: Although not usually on an AE listing, this helps support rechallenge argumentation, if needed, so can be useful.

12.1 ADVERSE EVENTS

Where AE summarisations are presented, the counting rules must be clearly explained (e.g. in a footnote). It should also be clearly stated if all AEs are included or just treatment-emergent AEs (TEAEs). The definition of a TEAE should be provided, for example, in Section 9.7 (Statistical Analysis Methods Planned in the Protocol and Determination of Sample Size). If there is a prior agreement with the regulatory authority to consider specified events differently, it should be documented, for example, in Section 7 (Introduction) and Section 9.5.1 (Efficacy and Safety Measurements Assessed and Schedule of Assessments). The tables should include changes in vital signs and any laboratory changes that were considered serious TEAEs or other significant TEAEs. If relevant to the study, pre- and post-study AEs can also be presented or referenced in the end-of-text Section 14 (Tables and Figures) tables.

The 'all AEs' tabular summarisation should be restricted to Section 14 (Tables and Figures) and referenced in-text. It should not be duplicated in the main CSR text. All TEAEs (including events likely to be related to the underlying disease or likely to represent concomitant illness) should be displayed in summary tables (Section 14.3.1 [Displays of Adverse Events]).

The end-of-text tables in Section 14 (Tables and Figures) should list each AE, the number of subjects in each treatment group in whom the event occurred and the rate of occurrence (i.e. AEs must be presented at both the subject and the event level). When treatments are cyclical, e.g. cancer chemotherapy, it may also be helpful to list results separately for each cycle. AEs should be grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class. Each event may then be divided into defined severity categories (e.g. mild, moderate, severe), or National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grades, if these were used. The tables may also divide the AEs into those considered at least possibly related to Investigational Product use and those considered not related, or use some other causality scheme (e.g. unrelated or possibly, probably or definitely related). Even when such a causality assessment is used, the tables should include all AEs, whether or not considered Investigational Product-related, including events thought to represent concurrent illnesses. It should be clear whether the causality assessment was made by the Investigator or by the Sponsor. Subsequent analyses of the study or of the overall safety database may help to distinguish between AEs that are, or are not, considered Investigational Product-related. So that it is possible to analyse and evaluate the data in these tables, it is important to identify each subject having each AE. An example of such an end-of-text tabular presentation is shown in Annex V.

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Comment [A418]: General information regarding treatment of AEs is in ICH E3 Sections 12.2.1 (Brief Summary of Adverse Events), 12.2.2 (Display of Adverse Events) and 12.2.3 (Analysis of Adverse Events), but actually applies to all AE sections. Therefore general information regarding treatment of AEs is moved to CORE Reference Section 12.1 (Adverse Events) since the text is applicable to all subsequent sub-sections.

Comment [A419]: The ICH E3 text 'treatment-emergent signs and symptoms (TESS)' has been replaced with the more common term 'treatment-emergent AEs (TEAEs)'.

Note that "TEAE" may be used in statistical output, but it is reasonable in the CSR text to use "AE", and define that as meaning treatment-emergent, for conciseness and readability.

Comment [A420]: Any prior agreement with the regulatory authority to consider specified events differently than TEAEs should be documented. Clarification is given to state that if there is a prior agreement with the regulatory authority to consider specified events differently, it should be documented, for example, in Section 9.5.1 (Efficacy and Safety Measurements Assessed and Schedule of Assessments) and in Section 7 (Introduction).

Comment [A421]: This table is often very long and can interrupt the flow of text in the CSR, so recommend it is placed in Section 14 if more than 1 page long. It may additionally be included in text if it is less than one page long.

Comment [A422]: 'Rate of occurrence' should prompt for events to be summarised at both the subject and event level. Clarification is given that both subjects and events should be summarised.

Comment [A423]: The ICH E3 term 'body system' is clarified, and the coding dictionary is named for clarity. See: http://meddra.org.

Comment [A424]: Clarification to allow for (commonplace) use of grades, and that the standard grading system for AEs is CTCAE. See: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Comment [A425]: Suggest to document in whose opinion causality is assigned. See note below on FDA perspective on causality assessment.

Comment [A426]: The entire paragraph is ICH E3 Section 12.2.2 (Display of Adverse Events) text with clarifications.

Comment [A427]: Relocation of the *in situ* tabular presentation to Annex V as this refers to an end-of-text table.

In presenting TEAEs, it is important both to display the original terms used by the Investigator (verbatim term) in the listings and to attempt to group related events (i.e. events that probably represent the same phenomena) in the summary tables, so that the true occurrence rate is not obscured. One way to do this is with a standard adverse reaction/events dictionary. The dictionary used, including version number, should be specified in a footnote to each listing or table. The MedDRA is a user-responsive technology. If dictionary terms do not fit study requirements, MedDRA encourages submission of a Change Request. See http://www.meddra.org/sites/default/files/page/documents/6282-330_changereq_info.pdf.

In all tabulations and analyses, TEAEs associated with both Test Product and Control Product should be displayed. In general, do not repeat in-text tabulated summary data by additionally describing all the details in text.

12.1.1 Brief Summary of Adverse Events

The overall AE experience in the study should be described in a brief narrative. Inclusion of a brief summary table is encouraged if this adds clarity, supported by more detailed tabulations and analyses.

The brief summary table should describe the overall AE experience in the study and should include the numbers of subjects with at least one TEAE, related TEAE and severe TEAE; and the numbers of subjects who died and who experienced a treatment-emergent SAE, or discontinued Investigational Product or withdrew from the study due to a TEAE. Relevant treatment group differences and trends with increasing dose should be mentioned.

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Comment [A428]: ICH E3 specifies 'AEs'. This is clarified as 'TEAEs'.

Comment [A429]: Consider for PPD impact: Verbatim text in the listings should not be presented in the text of the 'primary use CSR' for regulatory review, as verbatim text may present the opportunity for de-anonymisation of individual subjects. This recommendation is to help avoid the need for piecemeal redaction of 'primary use CSR' text, in the 'secondary use CSR' for public disclosure.

Comment [A430]: ICH E3 Section 12.2.2 (Display of AEs) text with clarifications.

Comment [A431]: Information communicated by MedDRA's Chief Medical Officer at May 2015 European Medical Writers Association conference, Expert Seminar Series entitled 'What Medical Writers Need to Know About MedDRA': Some Sponsors code AEs they deem to probably represent the same phenomena into a self-defined group. MedDRA strongly discourages this practice and instead encourages Change Request submission.

Comment [A432]: ICH E3 text says: 'In all tabulations and analyses, events associated with both test drug and control treatment should be displayed.' CORE Reference consistent terminology is applied here.

Comment [A433]: Often summary in-text table information is repeated in the CSR text. Clarification is added to indicate this should not be done but rather that a brief summary of the key findings should be noted in the text.

Comment [A434]: Descriptive text (i.e. the brief narrative) is often supported by a summary table in practice. A tabular presentation is encouraged as it adds clarity.

Comment [A435]: Suggest to present the more detailed tables and analyses in, for example, Section 12.1.2 (Most Frequently Reported Adverse Events) onwards.

Comment [A436]: For submissions in the US, FDA holds that the Sponsor should make final decisions on causality given their access to a complete dataset of safety data across multiple sites. See NEJM Perspective article from key FDA CDER leaders: http://www.nejm.org/doi/full/10.1056/NEJMp1103464 that explains the reporting regulation [21 CFR 312.32 (c) (A)]: http://www.ecfr.gov/cgi-bin/text-idx?SID=9661aeb85e493caed76a11faa6545dce&mc=true&node=se21.5.312_132&rgn=div8 associated with the (at that time) requirements for clinical trial safety reports.

Comment [A437]: Clarification on suggested content of the aforementioned brief narrative or summary table.

12.1.2 Most Frequently Reported Adverse Events

<Deliberate wider line spacing below to allow optimal presentation of ICH E3 2012 Q&A text>

The main presentation required is that of the most frequently reported TEAEs, regardless of relationship to treatment, at the subject and event level *comparing treatment and control groups, not including subject identifying numbers or verbatim AE terms*. The presentation should be limited to *relatively common* TE*AEs* (e.g. those in at least 1% or 5% of the treated group, or another defined threshold appropriate to the study).

12.1.3 Categorisation of All Adverse Events

The categorisation of AEs requires summarisations of all TEAEs by relationship/causality to Investigational Product, by severity, together with any other analyses of all TEAEs thought to be relevant. Categorisation of all TEAEs will facilitate review of AE occurrence in all treatment groups. For large studies, it may also be appropriate to present these analyses by the most frequently reported TEAEs.

The basic display of TEAE rates, located in Section 14.3.1 (Displays of Adverse Events) of the report, should be used to compare rates in treatment and control groups, combining the event severity categories and the relationship/causality categories, leading to a simpler side-by-side comparison of treatment groups.

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Comment [A438]: ICH E3 Section 12.2.2 (Display of Adverse Events) versus Section 12.2.3 (Analysis of Adverse Events): It is not sufficiently clear what content should be presented in each. Adaptation of the section titles, together with more explicit instruction on content is provided in line with ICH E3 2012 Q & A guidance.
This section summarises the main presentation of interest, namely the most frequently reported TEAEs.

Comment [A439]: See ICH E3 2012 Q & A Point 6 which clarifies that the full listing of AEs with subject IDs should NOT be included in the main CSR body. ICH E3 Q & A 2012 states: '*The body of the CSR …should include a summary table of relatively common adverse events – those occurring in at least a particular percentage of subjects who received the investigational drug. This summary tabulation compares treatment and control groups and does not include subject identifying numbers or verbatim adverse event terms*'. Note that ICH E3 2012 Q & A states that verbatim terms and subject IDs should be included in the listings. Further: '*Of note, the example table provided in Section 12.2.2 of the Guideline is not meant to be presented in Section 12.2.2 of the report, but in Section 14.3.1, which is not part of the text of the clinical study report*' where 'the Guideline' referred to is ICH E3.

Comment [A440]: As stated above, ICH E3 is not clear in what should be presented in ICH E3 Sections 12.2.2 and 12.2.3.
CORE Reference Section 12.1.3 (Categorisation of All Adverse Events) summarises ALL TEAEs, by relationship/causality and severity.

Comment [A441]: For submissions in the US, FDA holds that the Sponsor (rather than Investigator) should make final decisions on causality given their access to a complete dataset of safety data across multiple sites. See NEJM Perspective article from key FDA CDER leaders: http://www.nejm.org/doi/full/10.1056/NEJMp1103464 that explains the reporting regulation [21 CFR 312.32 (c) (A)]: http://www.ecfr.gov/cgi-bin/text-idx?SID=9661aeb85e493caed76a11faa6545dce&mc=true&node=se21.5.312_132&rgn=div8 associated with the (at that time) new requirements for clinical trial safety reports.

Comment [A442]: ICH E3 does not include a sub-section for discontinuations due to AEs and these may be grouped under 'Other Clinically Meaningful Adverse Events'. To include these in the main AE section is a perfectly reasonable approach. An alternative (shown below) is to pull discontinuations due to AEs out as a separate subsection leaving 'other clinically meaningful adverse events' to include other (marked) abnormalities.

Comment [A443]: ICH E3 specifies 'AEs'. Clarified as 'TEAEs' in this and subsequent paragraphs.

Comment [A444]: ICH E3 Section 12.2.3 text presented here is consolidated with no loss of meaning.

In addition, although this is usually best done as a pooled analysis across multiple studies, if study size and design permit, it may be useful to examine the more common TEAEs that seem to be Investigational Product-related for relationship to dosage and to mg/kg or mg/m^2 dose, to dose regimen, to duration of treatment, to total dose, to demographic characteristics (such as age, sex, race), to other baseline features (such as renal status), to efficacy outcomes and to Investigational Product concentration.

It may also be useful to examine time of onset and duration of TEAEs and describe prevalence over time. A variety of additional analyses may be suggested by the study results or by the pharmacology of the Investigational Product.

It is not intended that every TEAE be subjected to rigorous statistical evaluation. It may be apparent from initial display and inspection of the data that a relationship to demographic or other baseline features is not present. If the studies are small and if the number of events is relatively small, it may be sufficient to limit analyses to a comparison of Test Product and Control Product.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude TEAE rates. When treatments are cyclical, e.g. cancer chemotherapy, it may also be helpful to analyse results separately for each cycle.

Groups of AEs that might warrant further investigation should be mentioned.

Present a reference to the relevant named end-of-text AE listings in Appendix 16.2.7.

12.2 ANALYSIS OF DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER CLINICALLY MEANINGFUL ADVERSE EVENTS

Deaths, other serious AEs, and other clinically meaningful AEs – which may include discontinuations due to AEs and other AEs of special interest – deserve special attention.

12.2.1 Deaths, Other Serious Adverse Events, Discontinuations due to Adverse Events and Other Adverse Events of Special Interest

Relevant listings, containing the same information as described in, for example, Section 12 (Safety Evaluations), should be provided for deaths, other SAEs, and clinically meaningful AEs, which may include AEs leading to permanent discontinuation of Investigational Product and other AEs of Special Interest – in Section 14.3.2 (Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events).

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Comment [A445]: Clarified the ICH E3 term 'integrated analysis of safety'.

Comment [A446]: Can be an informative addition.

Comment [A447]: ICH E3 term 'significant' is omitted.

Comment [A448]: ICH E3 uses 'treatment and control'. Language is clarified here as 'Test Product and Control Product'. See Preface for terminology relating to Investigational Product.

Comment [A449]: This can be an informative addition. For example, if the Investigational Product might cause drowsiness, then all terms related to this, such as drowsiness, somnolence, feeling tired etc. can be discussed together.

Comment [A450]: ICH E3 Section 12.2.4 (Listing of Adverse Events by Subject) heading has been omitted as deemed not necessary for a CSR (ICH E3 text describes elements of subject listings which should be covered in the SAP). Note that the guidance text from that ICH E3 section is, however, contained in CORE Reference Section 12.

Comment [A451]: The word 'Analysis' at the beginning of the heading is from ICH E3 Section 12.3.3 (Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events) which is omitted.

The ICH E3 words 'and discussion' in the section title have been omitted so as not to replicate the content of the CSR Discussion section here.

Comment [A452]: The term 'significant' can have statistical connotations, so statements like 'other significant AEs' have been changed to 'other clinically meaningful AEs' throughout Section 12.

Comment [A453]: 'Other clinically meaningful AEs' may be split into 'discontinuations due to AEs' and 'other AEs of special interest' (which include marked haematological and other laboratory abnormalities and AEs leading to intervention, dose reduction or notable additional concomitant treatment) if this adds clarity.

Comment [A454]: Replacement of 'significant' with 'clinically meaningful'.

Comment [A455]: 'Other clinically meaningful AEs' may be split into 'discontinuations due to AEs' and 'other AEs of special interest' if this adds clarity.

Comment [A456]: Clarification to show the listings required and that these should be in Section 14 (Tables and Figures) and not in the CSR text.

12.2.1.1 Deaths

All deaths during the study, including the pre-treatment (Screening) period, post-treatment follow-up period, and deaths that resulted from a process that began during the study, should be listed by subject in Section 14.3.2 (Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events). Consider distinguishing deaths that are the result of an AE (automatically an SAE) from deaths due to disease progression (this is permissible in some studies, e.g. studies where death is an endpoint). Describe deaths as the data allows. If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

12.2.1.2 Other Serious Adverse Events

All SAEs (other than death but including the SAEs temporally associated with or preceding the deaths) should be listed in Section 14.3.2 (Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events). The listing should include laboratory abnormalities, abnormal vital signs and abnormal physical observations that were considered SAEs. Describe (non-death) SAEs as the data allows. If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

12.2.1.3 Discontinuations Due to Adverse Events

Discontinuations of Investigational Product due to AEs should be described. In some cases it may be relevant to separate out AEs leading to discontinuation of Investigational Product (i.e. Test Product or Control Product) and AEs leading to withdrawal of the subject from the study.

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Comment [A457]: See ICH E3 2012 Q & A Point 5 on deaths: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf which states '*It is true that the structure and definitions provided in the ICH E3 Guideline could result in deaths appearing in Section 12.3.1.2 (as per E3 numbering), Other Serious Adverse Events, if an event terminated with, or was associated with, a subject's death. However, this should not result in double- or mis-counting of deaths. Although deaths may or may not be included in the listing for* ICH E3 *Section 12.3.1.2, all deaths should be captured in the listing for ICH E3 Section 12.3.1.1. That is, any subject death reported under Section 12.3.1.2 as an "other serious adverse event" with a fatal outcome would also have been captured under deaths in Section 12.3.1.1*'. So, ICH E3 2012 Q & A explains potential for double count.

The authors of CORE Reference recognise this as an area that requires individual Sponsor interpretation.

Comment [A458]: ICH E3 text does not specify if deaths before the initiation of the study treatment should be listed. This is clarified to indicate that deaths before initiation of study treatment should also be mentioned.

Comment [A459]: Replacement of 'significant' with 'clinically meaningful'.

Comment [A460]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A461]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A462]: ICH E3 does not include a sub-section for discontinuations due to AEs and these have tended to be grouped under ICH E3's 'Other Significant Adverse Events'. This is a perfectly reasonable approach. An alternative (shown here) is to pull discontinuations due to AEs out as a separate sub-section leaving 'other AE of special interest' to include other (marked) abnormalities. See below.

12.2.1.4 Other Adverse Events of Special Interest

Marked haematological and other laboratory abnormalities (other than those meeting the definition of serious), and events that led to an intervention, including dose reduction or those that needed notable additional concomitant therapy (other than those reported as serious), should be listed in Section 14.3.2 (Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events). Sponsor-defined AEs of special interest may also be described here. Describe other AEs of special interest as the data allows. If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

12.2.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Clinically Meaningful Adverse Events

There should be brief clinical narratives describing each death and each other SAE, unless it has been pre-agreed with the regulatory authority that narratives are not needed in some cases (e.g. deaths due to underlying disease or in studies where death is an endpoint). In cases of Regulatory Authority waiver or non-applicability, this should be explained.

Narratives for discontinuations due to AEs and those of the other clinically meaningful adverse events that are judged to be of special interest because of clinical importance should also be provided, as appropriate.

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Comment [A463]: See 'Rationale' comment immediately above.

Comment [A464]: Clarification of ICH E3 text.

Comment [A465]: Note the omission of ICH E3 text: '… including withdrawal of test drug/investigational product treatment…' because this is covered in, for example, Section 12.2.1.3 (Discontinuations due to adverse events) above.

Comment [A466]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A467]: Replacement of 'significant' with 'clinically meaningful'.

Comment [A468]: Added 'clinical' to show that these are not 'safety' narratives (see below).

Comment [A469]: Health Canada, agree with the 'pre-agreement' CORE Reference clarification, adding that '…it is generally understood that deaths do not need to be reported in an expedited manner during the conduct of the trial where the death occurred due to disease progression. The reasons for each death still need to be captured clearly in study documents (e.g. CRF), and summarised in the CSR, but a narrative would not be expected. There should be an explanation of the scope of the narratives included in the CSR text'.

Comment [A470]: Replacement of 'significant' with 'clinically meaningful'.

These narratives should be subject-based and can be placed either in the text of the report or in Section 14.3.3, depending on their number. Events that were clearly unrelated to the Test Product may be omitted or described very briefly. In general, the narrative should describe the following: the nature and intensity of event, the clinical course leading up to event, with an indication of timing relevant to Investigational Product administration, relevant laboratory measurements, whether the Investigational Product was stopped and when, countermeasures, event outcome, post mortem findings, Investigator's opinion on causality and Sponsor's opinion on causality, if appropriate.

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Comment [A471]: There is a need to distinguish between 'safety' narratives (per Suspect Adverse Reaction Reports required for direct regulatory reporting: e.g. CIOMS: http://www.cioms.ch/index.php/cioms-form-i and MedWatch http://www.fda.gov/Safety/MedWatch/) and 'clinical' narratives (per CSR). Currently, some Sponsors reconcile the safety/pharmacovigilance database with the clinical database and provide the final Suspect Adverse Reaction Reports (CIOMS or MedWatch) in place of writing clinical CSR narratives. The difference between the two types of narratives is that the Suspect Adverse Reaction Reports are event-based and can have a string of updated information included as more information becomes available. In contrast, clinical CSR narratives are subject-based, and only the final information is presented. The widespread practice of including (clinical database reconciled) Suspect Adverse Reaction Reports in place of writing CSR narratives is therefore questionable and requires definitive instruction.

Note that Health Canada agree with subject-based narratives, adding that they '...should be comprehensive and include all the necessary information to present the full picture of the case. Sponsors may not comply with the request to include subject-based narratives, such as for very large trials with many narratives'.

Comment [A472]: Consider for PPD impact: ICH E3 states that narratives may be placed in Section 12.3.2 (i.e. integral to the main CSR text; CORE Reference Section 12.2.2) or in Section 14.3.3 (i.e. in the end-of-text tables section, subordinate to the main CSR text). Suggest that placement in Section 14.3.3 could ease redaction in the 'secondary use CSR' for public disclosure in regions where the entire Section could be redacted. Note that in the EU, March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf. Chapter 2, Section 2.2) which states that 'Case narratives should not be removed or redacted in full regardless of their location within the clinical reports (body of the report or listings). They should be instead anonymised'.

For narratives it is particularly important to consider data presentations that maintain data meaning, remain in context AND conform to current minimum standards for de-identifying data.

In regions where full narrative redaction is not allowed (i.e. EU), for studies with large numbers of narratives, the narratives should be placed in Section 14.3.3 so as not to interrupt the flow of CSR text.

Comment [A473]: ICH E3 'test drug/ investigational product' clarified as 'Test Product'.

Comment [A474]: Modified from 'Test Drug/ Investigational Product'.

Comment [A475]: Modification of ICH E3 term 'drug' to appropriate CORE Reference terminology.

Comment [A476]: Added 'outcome'.

Additional information can be obtained from the event-based Suspect Adverse Reaction Report, but these event-based safety narratives should not be used in place of the subject-based clinical narratives, even if the source safety/pharmacovigilance database is reconciled with the definitive study reporting clinical database.

In addition, the following narrative information, which may be tabulated, should be included:

- Subject identifier
- Age and sex of subject; general clinical condition of subject, if appropriate
- Disease being treated (if the same for all subjects, this is not required) with duration (of current episode) of illness
- Relevant concomitant/previous illnesses with details of occurrence/duration
- Relevant concomitant/previous medication with details of dosage
- Investigational Product administered, and dose, if this varied among subjects, and length of time administered.

If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

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Comment [A477]: e.g. CIOMS: http://www.cioms.ch/index.php/cioms-form-i or MedWatch forms: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

Comment [A478]: To allow for tabulation of certain narrative information at the beginning of each narrative in order to ease reader comprehension.

Comment [A479]: Modification of ICH E3 term 'Test Drug/investigational Product' to appropriate CORE Reference terminology.

Comment [A480]: Omitted ICH E3 word 'drug'.

Comment [A481]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A482]: Consider for PPD impact: One particular example of how careful narrative data presentation in the 'primary use CSR' can maintain data meaning, remain in context AND conform to current minimum standards for de-identifying data follows:

Calendar dates for narrative events would not be allowed in the 'secondary use CSR' for public disclosure as these may increase the chance of subject re-identification. In the 'primary use CSR' for regulatory review, only refer to study days and do not refer to calendar dates. This approach captures event timing (necessary to inform the assessment of temporal association) in the 'primary use CSR' without increasing redaction need in the 'secondary use CSR'.

Note however, that this may need special consideration for some illnesses where dates can be important, for example, allergy and seasonal affective disorder where alternative presentations should be considered that still avoid the actual date.

Comment [A483]: ICH E3 Section 12.3.3 (Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events) has been omitted as this separate subsection was not deemed necessary in light of the suggested content included in, for example, Section 12.2 above.

12.3 CLINICAL LABORATORY EVALUATION

12.3.1 Individual Laboratory Measurements by Subject and Abnormal Laboratory Values

Cross-reference to the relevant named end-of-text laboratory listings in Section 14 (Tables and Figures).

12.3.2 Evaluation of Laboratory Values

The necessary evaluation of laboratory values must in part be determined by the results seen, but, in general, the following analyses should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate, and as compatible with study size.

If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

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Comment [A484]: ICH E3 Section 12.4.1 title mentions 16.2.8 and 14.3.4, but these may add confusion so have been omitted, as has the word 'Listing" from the title of this section.
This entire section actually relates to the end text Appendix 16.2 listings, so all that is ever included in CSR text per ICH E3 Section 12.4.1 (Listing of Individual Laboratory Measurements by Patient and Abnormal Laboratory Values) is a cross-reference to the Appendix 16.2 listings. The text is moved to Annex IV because it informs statisticians on how to present the laboratory data listings, and is not relevant directly to creation of CSR text.
Consider for PPD impact:
March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 87 of 91 states:
'EMA notes that under ICH E3, the CSRs may contain individual patient data listings … even within the body of the report. For example, these … may be contained in CSR section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit), as well as elsewhere in the CSR body … EMA considers that such per patient/per visit line listings fall outside the scope of phase 1 of the Policy [0070] and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy.'
Per page 6 of 91, Policy 0070 is in two phases. Phase 1 (01 January 20 pertains to publication of CSRs only. Phase 2, which will be implemented at a later stage, pertains to the publishing of individual patient data.

Comment [A485]: The text in ICH E3 Section 12.4.1 relates to Appendix 16.2 listings, and not to what should appear in CSR text. The text is therefore relocated to Annex IV Section C.

Comment [A486]: ICH E3 Section 12.4.2 title (Evaluation of Each Laboratory Parameter) is adapted.

Comment [A487]: Consider for PPD impact: In case individual cases are described in the 'primary use CSR', protect subject anonymity in the 'secondary use CSR' for public disclosure.
Also consider the possibility that individual subject laboratory numerical data in the 'primary use CSR' may, in the 'secondary use CSR', require full redaction or modification by substitution with more general text such as 'elevated', 'normalised' etc. This will depend on the individual Sponsor.

Comment [A488]: ICH E3 text 'In addition, normal laboratory ranges should be given for each analysis.' has been omitted as it is not possible to ascribe normal ranges for analyses – i.e. summary laboratory data. Normal ranges can only ever apply to individual subject results. This is mentioned in Annex IV.

Comment [A489]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Within each of the following topic areas (see for example Section 12.3.2.1 [Laboratory Values Over Time], Section 12.3.2.2 [Individual Subject Changes in Laboratory Values] and Section 12.3.2.3 [Individual Clinically Meaningful Laboratory Abnormalities]), it may add clarity to separate haematology, chemistry and urinalysis, or any other laboratory test categories applicable to the study. Alternatively, present all analyses for a particular category of laboratory values first followed by similar presentations for the other categories.

12.3.2.1 Laboratory Values Over Time

For each parameter at each time over the course of the study (e.g. at each visit) the following should be described: the group mean or median values and/or change from baseline (absolute or percentage change as appropriate to the data) over time, and the range of values. Note any change within the treatment groups over time. Note relevant treatment group differences. Graphical presentation of laboratory values may be used and can be preferable, especially where the number of samples allows for such a presentation.

12.3.2.2 Individual Subject Changes in Laboratory Values

An analysis of individual subject changes by treatment group should be given. A variety of approaches may be used, including:

1. "Shift tables" – These tables show the number of subjects who are low, normal or high at baseline and then at selected time intervals. These selected time intervals may be scheduled visits or a derived timepoint such as the most extreme on-treatment value. If applicable, laboratory results may be categorised based on NCI CTCAE grades.

2. Tables showing the number or proportion of subjects who had a change in parameter of a predetermined size at selected time intervals. For example, for blood urea nitrogen (BUN), it might be decided that a change of more than 10 mg/dL BUN should be noted, or laboratory values twice the upper limit of normal, five times the upper limit etc. (choices should be explained). For this parameter, the number of subjects having a change less than this or greater than this would be shown for one or more visits, usually grouping subjects separately depending on baseline blood urea nitrogen (BUN) (normal or elevated). The possible advantage of this display, compared to the usual shift table, is that changes of a certain size are noted, even if the observed value is not abnormal.

3. A graph comparing the initial value and the on-treatment values of a laboratory measurement for each subject by locating the point defined by the initial value on the abscissa and a subsequent value on the ordinate. If no changes occur, the point representing each subject will be located on the 45° line. A general shift to higher values will show a clustering of points above the 45° line. As this display usually shows only a single time point for a single treatment, interpretation requires a time series of these plots for treatment and control groups. Alternatively, the display could show baseline and a derived timepoint such as most extreme on-treatment value. Data may be presented using the observed values or may be expressed as multiples of the normal range limits. These displays identify outliers readily (it is useful to include subject identifiers for the outliers). Discussion of these outputs should mention common (≥XX% subjects) shifts in the active treatment group from normal at baseline to an abnormal result post-baseline at the timepoint of interest. The focus should be on laboratory changes that are clinically

Comment [A490]: The structure for content in ICH E3 Section 12.4.2 (Evaluation of Each Laboratory Parameter) is not clear. CORE Reference suggests content breakdown into hematology, chemistry and urinalysis within each of the 3 examples (Section 12.3.2.1-12.3.2.3). Alternatively, present all analyses for haematology values first (means over time, shifts, potentially clinically meaningful abnormalities) followed by similar presentations for chemistry and urinalysis parameters.

Comment [A491]: ICH E3 text on upper limits is relocated more appropriately to the content of the section below.

Comment [A492]: Clarification on detail of data presentation is provided.

Comment [A493]: Clarification that use of graphs, which can be visually more informative than tables, if sample numbers allow – is acceptable.

Comment [A494]: Health Canada recommend keeping reference to shift tables, although reportedly many medical writers question their value.

Comment [A495]: ICH E3 instructional text does not state if the worst value or last value is of interest here. Clarified to suggest that worst value (most extreme on-treatment assessment) is of interest in most cases.

Comment [A496]: ICH E3 text does not mention that shifts in CTCAE toxicity grades may also be explored. Clarification is added.

Comment [A497]: Clarification of the ICH E3 term 'fraction of patients'.

Comment [A498]: Clarification to suggest shifts of interest (detail is included in ICH E3 text under Section 12.4.2.1 (Laboratory Values Over Time) but is more appropriately placed here.

Comment [A499]: Expansion of the existing detail on graphical presentations as it did not specify the values that might be presented, e.g. may use values expressed as multiples of normal range limits.

Comment [A500]: Consider for PPD impact: In-text presentations of such displays must give careful consideration to inclusion of subject identifiers (which should not include centre identifier or any other information that could potentially compromise subject anonymity). Care with presentation in the 'primary use CSR' for regulatory review will minimise the need for redaction in the 'secondary use CSR' for public disclosure.

Comment [A501]: Clarification to distinguish between values outside the normal laboratory range compared to clinically meaningful values and changes.

meaningful. Relevant treatment group differences that raise potential safety issues should also be discussed.

12.3.2.3 Individual Clinically Meaningful Laboratory Abnormalities

Clinically meaningful changes (defined by the Sponsor) should usually be discussed. A narrative of each subject whose laboratory abnormality was considered an SAE and, in certain cases, led to discontinuation of Investigational Product or was considered to be an 'other clinically meaningful AE', should be provided under Section 12.2.2 or Section 14.3.3.

Two common approaches are used to assess individual clinically meaningful abnormalities. A clear description of the approach used is required:

The first approach uses Sponsor-defined abnormality criteria or an established toxicity grading scale such as the NCI CTCAE (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) When toxicity grading scales are used (e.g. NCI CTCAE), changes graded as at least severe (Grade 3 or above) should be discussed regardless of seriousness.

The second approach uses the Investigator's assessment of whether an abnormal value was clinically meaningful or not (usually a check box next to the laboratory abnormality in the CRF). In this case, the same abnormality may be judged clinically meaningful for one subject but not for another by the same Investigator, and may be judged clinically meaningful by one Investigator but not by another.

An in-text table with a list of subjects with clinically meaningful changes should be sourced from the by-subject listing of all abnormal laboratory values in Section 14.3.4 (Abnormal Laboratory Values Listing [Each Subject] – see Annex VI) and presented in text. An analysis of clinically meaningful changes, together with a recapitulation of discontinuations due to laboratory measurements, should be provided for each parameter. The trends and importance of any changes and likely relation to the Investigational Product should be assessed, e.g. by analysis of such features as relationship to dose, relationship to Investigational Product concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge and the nature of concomitant therapy.

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Comment [A502]: ICH E3 term 'significant' is standardised to 'meaningful' in CORE Reference.

Comment [A503]: Clarification: added the word 'usually' because it may not always be informative or necessary to discuss such changes, for example, in a liver cancer study, it would not be expected to discuss all Grade 3 elevated liver function test values.

Comment [A504]: Consider for PPD impact: ICH E3 states that narratives may be placed in Section 12.3.2 (i.e. integral to the main CSR text; CORE Reference Section 12.2.2) or in Section 14.3.3 (i.e. in the end-of-text tables section, subordinate to the main CSR text). Suggest that placement in Section 14.3.3 could ease redaction in the 'secondary use CSR' for public disclosure in regions where the entire Section could be redacted. Note that in the EU, March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf. Chapter 2, Section 2.2) which states that 'Case narratives should not be removed or redacted in full regardless of their location within the clinical reports (body of the report or listings). They should be, instead, anonymised.'
For narratives it is particularly important to consider data presentations that maintain data meaning, remain in context AND conform to current minimum standards for de-identifying data. In regions where full narrative redaction is not allowed (i.e. EU), for studies with large numbers of narratives, the narratives should be placed in Section 14.3.3 so as not to interrupt the flow of CSR text.

Comment [A505]: Grading of laboratory events: the alternatives of Sponsor-defined or official grading scale (NCI CTCAE) versus Investigator assessment of clinical significance is explained for clarity, including (in the next paragraph) the need to capture abnormal clinically meaningful laboratory values at the time they arise (in the CRF).

Comment [A506]: Omission of 'WHO' and addition of 'CTCAE' for clarity.

Comment [A507]: This table (in reality a listing) may be far too long to place in-text for a late-phase study. If very long, the overview that it is meant to provide can be lost. Unless there are unusual findings, consider that this table/listing might be better left out of the CSR text. The decision will be study-dependent.

Comment [A508]: ICH E3 wording: 'The significance of the changes and likely relation to the treatment should be assessed' is clarified.

The ICH E3 word 'significance' is substituted here with 'importance'.

If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

12.4 VITAL SIGNS, PHYSICAL EXAMINATIONS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs, physical examinations and other observations related to safety should be analysed and presented in a way similar to laboratory values. If there is evidence of an Investigational Product effect, any dose-response or Investigational Product concentration-response relationship or relationship to subject variables (e.g. disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be AEs.

If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

Example sub-sections may be as follows:

12.4.1 Vital Signs

Vital signs data may be described as for laboratory data, namely vital signs over time, individual subject changes and individual clinically meaningful abnormalities, if applicable.

12.4.2 Physical Examination Findings

Physical findings may be described noting treatment group differences and trends with increasing dose, if applicable.

12.4.3 Other Observations Related to Safety

Examples of safety assessments discussed may include: ECG, electroencephalography, x-ray, etc. The results may include means over time, shifts, incidence of marked/clinically meaningful abnormalities, etc. depending on the type of analyses used.

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Comment [A509]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A510]: Consider for PPD impact: Also consider the possibility that individual subject laboratory numerical data in the 'primary use CSR' may, in the 'secondary use CSR', require full redaction or modification by substitution with more general text such as 'elevated', 'normalised' etc. This will depend on the individual Sponsor.

Comment [A511]: ICH E3 title states physical 'findings'; 'examinations' is suggested as more appropriate to the content of the section.

Comment [A512]: 'Other' is omitted as considered redundant.

Comment [A513]: 'Variables' is substituted with 'values' for clarity.

Comment [A514]: Suggest to cross-reference to Section 12.1 (Adverse Events) for those considered to be AEs.

Comment [A515]: Consider for PPD impact: Consideration of data presentations that achieve anonymity in the 'primary use CSR' for regulatory review will minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A516]: Consider for PPD impact: Also consider the possibility that individual subject numerical data in the 'primary use CSR' may, in the 'secondary use CSR', require full redaction or modification by substitution with more general text such as 'elevated', 'normalised' etc. This will depend on the individual Sponsor.

Comment [A517]: Suggested structure is included to support this using example sub-sections for applicable parameters below.

12.5 SAFETY RESULTS SUMMARY

Include a bullet list summarising the main safety results of the study, and without interpretation or drawing of conclusions.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1 DISCUSSION

A good discussion section examines the implications of the data.

Explain any limitations of the trial, e.g. short treatment period, difficult to follow protocol, sources of potential bias and imprecisions that led to deviations and inconsistencies (e.g. delays in delivery of supplies to sites, large numbers of subjects in one or more sites that were not familiar with local language etc.).

If a structured benefit-risk methodology was used, this should be noted. If allowed concomitant therapy affected the outcome (see, for example, Section 9.4.6 [Prior and Concomitant Therapy]) due either to drug-drug interaction or to direct effects on the study endpoints, discuss this and explain how the independent effects of concomitant and study therapies were ascertained.

The efficacy and safety results of the study and the relationship of risks and benefit should be briefly summarised and discussed, referring to specific data from the in-text tables, in-text figures and sections above as needed. Where data are referred to, there should be no cross-referencing to the CSR results sections. Instead, the actual data should be briefly presented in the text of, for example, Section 13 (Discussion and Overall Conclusions), alongside any discussion. The presentation should not simply repeat the description of results nor introduce new results, but explain what the results mean or what they may imply. The conduct of any relevant *post-hoc* analyses may be mentioned (clearly stating that the results are *post-hoc*), together with an explanation of their relevance for the current study results.

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Comment [A518]: ICH E3 Section 12.6 (Safety Conclusions) content often results in overlap of content with Section 13. Discussion and Overall Conclusions section, probably because of wording of the titles.

Clarity is required on how best to avoid content duplication of ICH E3 Sections 12.6 and 13, and on how to end up with a more detailed Discussion and Conclusions section in Section 13.

Suggest the inclusion of 'Efficacy Results Summary' and 'Safety Results Summary' sub-sections, directly after the respective main results sections. Note that these example suggested sections do not include the word 'conclusions' and should not include any interpretation or conclusions but should merely (bullet) summarise the main results. Such summaries are useful for writing the Synopsis and other related sections (e.g. Discussion and Overall Conclusions).

It should be noted that these example sub-sections may be omitted if desired. The important point is NOT to have conclusions drawn in 2 separate places in the report.

Comment [A519]: Discussion and conclusion sections may be merged if preferred. Here a suggestion is made to separate the two.

Comment [A520]: Added to provide clarification of the detail about benefit-risk assessment to include in the Discussion. The underlined text from the following ICH E3 extract is relocated from ICH E3 Section 11.4.1 (Analysis of Efficacy) as it is more appropriately placed in the Discussion: 'Treatment groups should be compared for all critical measures of efficacy (primary and secondary end-points; any pharmacodynamic end points studied), as well as benefit/risk assessment(s) in each patient where these are utilised'. Further, the underline text is paraphrased.

Comment [A521]: ICH E3 Section 9.4.7 (Prior and Concomitant Therapy) text is relocated more appropriately here to ensure discussion about possible drug interactions is not overlooked. Minor changes to the wording do not affect the meaning.

Comment [A522]: ICH E3 is unclear if referencing tables, figures and other sections within Section 13 (Discussion and Overall Conclusions) is acceptable - clarification that specific data from the preceding CSR sections may be presented in Section 13 if discussed in this section. Further clarification that Section 13 should stand alone without cross-reference to other CSR sections.

Comment [A523]: Addition to ensure relevant *post-hoc* findings are placed into context.

The discussion and conclusions should clearly identify any new or unexpected findings (without presenting any results not already presented in the CSR text sections above), comment on their importance and discuss any potential problems such as inconsistencies between related measures. The clinical relevance and importance of the results should also be discussed in the light of other relevant existing data. Without including a complete review of the therapeutic area, results should be placed in context with all relevant existing data. Any specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies should be identified. The impact of exclusions on the generalisability of the study should be discussed. Alternatively, such discussions may be reserved for summaries of safety and efficacy referring to the entire dossier (integrated summaries). The discussion section should be between two and five pages in length (although may be longer if there are multiple issues to address or shorter for early development studies).

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Comment [A524]: Reminder to not introduce new data not presented in the main CSR text.

Comment [A525]: ICH E3 term 'significance' is changed here to 'importance'.

Comment [A526]: Item required by Annex IV Section A of the Clinical Trials Regulation EU No. 536-2014: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
See full explanation in CORE Reference Section 2: 'For clinical studies replicating studies on already authorised investigational products and used in accordance with the terms of the marketing authorisation, indicate identified concerns in the overall results of the clinical study relating to relevant aspects of the efficacy of the investigational product.' Omit for non EU studies.

Comment [A527]: Claims of benefit for not statistically significant 'trends' are discouraged.

Comment [A528]: Clarification that 'existing data' can mean published literature as well as information from other studies/CSRs.

Consider for CCI impact: Unpublished data and data already in the public domain cannot be redacted in the 'secondary use CSR' for public disclosure.

Refer to the EMA guidance (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf page 53 of 91) for irrelevant justification of proposed redactions.

Comment [A529]: Clarification is added that although it is necessary to include explanations for unexpected/inconsistent results, there should not be a presentational review of the therapeutic area - that is not within the scope of the discussion and conclusions content.

Comment [A530]: ICH E3 Section 9.3.2 (Exclusion Criteria) text is included here to avoid inadvertent omission from the discussion.

Comment [A531]: Suggested length of discussion, with regard for phase of and complexity of study.

The importance of deaths, other SAEs and clinically meaningful AEs leading to discontinuation of Investigational Product, dose reduction or institution of concomitant treatment should be assessed with respect to the safety of the Investigational Product. 'Other clinically meaningful AEs' may also include those of particular relevance because of clinical importance, depending on the treatment and the indication. Particular attention should be paid to whether any of these events may represent a previously unsuspected important adverse effect of the Investigational Product. For SAEs that appear of particular importance, it may be useful to use analyses to show their relation to time on Investigational Product and to assess their risk over time.

13.2 CONCLUSIONS

Conclusions should address the objectives of the study. They should be supported by the data in the report, taking into account statistical power considerations.

The important conclusions concerning efficacy should be concisely stated in one or two short paragraphs. Any relevant *post-hoc* analysis conclusions may be presented but must be clearly indicated as being based on *post-hoc* analyses that must be interpreted with caution.

The overall safety evaluation of the Test Product should be determined, with particular attention to events resulting in changes of dose or need for concomitant medication, SAEs, events resulting in discontinuation or withdrawal, and deaths. Any subjects or subject groups at increased risk should be identified and particular attention paid to potentially vulnerable subjects who may be present in small numbers, e.g. children, pregnant women, frail elderly, people with marked abnormalities of drug metabolism or excretion etc. There is a need to consider genetic markers, particularly if they predispose the subject to respond or to be resistant to the Test Product, or to experience SAEs. The implication of the safety evaluation for the possible uses of the Test Product should be described. Numerical data should not be specified in detail, but rather the overall conclusions should be drawn from these data.

Consider using bullet points for each objective/endpoint to ensure that the conclusions are clear and concise and that each objective/endpoint is addressed.

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Comment [A532]: ICH E3 term 'significance' is changed here to 'importance'.

Comment [A533]: Substitution of 'other significant' with 'clinically meaningful' to align terms with Section 12.

Comment [A534]: Clarification of ICH E3 text 'withdrawal'.

Comment [A535]: ICH E3 text is relocated here from ICH E3 Section 12.3.3 Analysis and discussion of deaths etc., as is more appropriately placed here.

Comment [A536]: ICH E3 text '…life tables or similar…' is omitted from here.

Comment [A537]: ICH E3 text is relocated here from ICH E3 Section 12.3.3 Analysis and discussion of deaths etc., as is considered to be more appropriately placed here.

Comment [A538]: Clarification: whether or not planned exploratory objectives are included may vary across studies.

Comment [A539]: Suggested length is given.

Comment [A540]: ICH E3 Section 11.4.7 (Efficacy Conclusions) text '…considering primary and secondary end points, pre-specified and alternative statistical approaches and results of exploratory analyses' may be too prescriptive, so is omitted. Given the suggestion on length, it is likely that key endpoints only could be covered. Conclusions may be drawn on *post-hoc* analyses and this is clarified.

Comment [A541]: ICH E3 word 'reviewed' is substituted with 'determined'.

Comment [A542]: ICH E3 Section 12.6 (Safety Conclusions) text.

Comment [A543]: Consider genetic markers here, particularly if they predispose the subject to respond or to be resistant to Investigational Product, or to experience SAEs.

Comment [A544]: ICH E3 Section 12.6 (Safety Conclusions) text.

Comment [A545]: The bullet list may be directly copied to the Synopsis Conclusions.

14. TABLES AND FIGURES

Figures should be used to visually summarise the important results or to clarify results that are not easily understood from tables.

Important demographic, efficacy, safety data and any other data relevant to the study should be presented in summary tables or figures in the text of the report. All data presented in the CSR text must be available in Section 14 (Tables and Figures) and/or Appendix 16.2 (Subject Data Listings), and all tables and figures provided in Section 14 (Tables and Figures) should be referenced in the CSR. Tables and figures in Section 14 (Tables and Figures) that are not presented in the CSR text, because they are considered obtrusive because of size or number, should be presented here, cross-referenced in the text, along with supportive or additional figures, tables or listings.

The following information may be presented in this section of the core CSR; the following example sub-sectioning may be used:

14.1 DEMOGRAPHIC DATA

Summary tables and figures.

14.2 EFFICACY DATA

Summary figures and tables.

14.3 SAFETY DATA

Summary figures and tables.

14.3.1 Displays of Adverse Events

All AEs occurring after initiation of study treatments (including events likely to be related to the underlying disease or likely to represent concomitant illness, unless there is a prior agreement with the regulatory authority to consider specified events as disease related) should be displayed in summary tables (Section 14.3.1). The tables should include changes in vital signs and any laboratory changes that were considered SAEs or other clinically meaningful AEs.

In most cases, it will also be useful to describe TEAEs in such tables.

14.3.2 Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events

Any listings information presented in this section of the 'primary use CSR' for regulatory review should fully support the review process. Listings data presented in this section in the 'secondary use CSR' for public disclosure should conform to **current** minimum standards for de-identifying data through piecemeal redaction, or may be fully redacted, depending on current requirements of the region.

ICH E3 text | *ICH E3 2012 Q&A text* | CORE Reference text | [Right margin comment=RATIONALE]

Comment [A546]: ICH E3 Section 14 title (Tables, Figures and Graphs Referred To But Not Included In The Text) may be interpreted that some tables presented in the CSR text may be omitted from Section 14 as they are already presented in text.
The title of this section is therefore clarified by omitting '…referred to but not included in the text'. 'Figures' also covers both 'figures and graphs' so 'graphs' is omitted.

Comment [A547]: Consider for PPD impact: All aggregated data in the 'primary use CSR' should be evaluated for possible redaction in the 'secondary use CSR' for public disclosure. See Preface for explanation about the risk of de-anonymisation from aggregated data.

Comment [A548]: 'core' used here is an ICH E3 word – meaning the 'text part' of the CSR.

Comment [A549]: Suggest flexibility regarding placement of Tables and Figures. They are not always broken up into these specified sections and may be provided as one PDF file.

Comment [A550]: Consider for PPD impact: EMA does not consider 'aggregated data' as PPD and will not allow redaction in the 'secondary use CSR' (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf page 87 of 91).
'EMA would like to emphasize that CSR sections:
14.3.1 Displays of Adverse Events
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events
DO FALL in the scope of the policy and SHOULD NOT BE REMOVED from the CSRs that are prepared for publication.'

Comment [A551]: Text paragraph is wholly relocated here from ICH E3 Section 12.2.2 (Display of Adverse Events).

Comment [A552]: The ICH E3 text 'treatment-emergent signs and symptoms (TESS)' has been replaced with the more common term 'treatment-emergent AEs (TEAEs)'. The definition of a TEAE should be provided, for example, in Section 9.7 (Statistical Analysis Methods Planned in the Protocol and Determination of Sample Size).
ICH E3 defines "treatment emergent signs and symptoms" (TESS; those not seen at baseline, and those that worsened even if present at baseline).'

Comment [A553]: The final text paragraph before the sample table in ICH E3 Section 12.2.2 (Displays of Adverse Events) 'The tables should list each AE…' is relocated (and modified) to CORE Reference Section 12.1 and the example table is shown in Annex V.

Comment [A554]: In ICH E3 terminology is 'significant'. Terminology standardised to 'clinically meaningful'.

14.3.3 Narratives of Deaths, Other Serious Adverse Events and Certain Other Clinically Meaningful Adverse Events

Narratives may be presented in this section.

If it is necessary to discuss any individual subject level information in text, consider data presentations that maintain data meaning, remain in context AND conform to **current** minimum standards for de-identifying data.

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Comment [A555]: In ICH E3 terminology is 'significant'. Terminology standardised to 'clinically meaningful'.

Comment [A556]: Also see full information on creation of narratives in Section 12.2.2 (Narratives of Deaths, Other Serious Adverse Events and Certain Other Clinically Meaningful Adverse Events).

Comment [A557]: Consider for PPD impact: ICH E3 states that narratives may be placed in Section 12.3.2 (i.e. integral to the main CSR text; CORE Reference Section 12.2.2) or in Section 14.3.3 (i.e. in the end-of-text tables section, subordinate to the main CSR text). Suggest that placement in Section 14.3.3 could ease redaction in the 'secondary use CSR' for public disclosure in regions where the entire Section could be redacted. Note that in the EU, March 2016 EMA guidance on use of Policy 0070. (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf. Chapter 2, Section 2.2) which states that 'Case narratives should not be removed or redacted in full regardless of their location within the clinical reports (body of the report or listings). They should be instead anonymised'

In regions where full narrative redaction is not allowed (i.e. EU), for studies with large numbers of narratives, the narratives should be placed in Section 14.3.3 so as not to interrupt the flow of CSR text.

Comment [A558]: Consider for PPD impact: One particular example of how careful narrative data presentation in the 'primary use CSR' can maintain data meaning, remain in context AND conform to current minimum standards for de-identifying data follows:

Calendar dates for narrative events would not be allowed in the 'secondary use CSR' for public disclosure as these may increase the chance of subject re-identification. In the 'primary use CSR' for regulatory review, only refer to study days and do not refer to calendar dates. This approach captures event timing (necessary to inform the assessment of temporal association) in the 'primary use CSR' without increasing redaction need in the 'secondary use CSR'.

Note however, that this may need special consideration for some illnesses where dates can be important, for example, allergy and seasonal affective disorder where alternative presentations should be considered that still avoid the actual date.

14.3.4 Data Listings (Each Subject) for Abnormal Clinically Meaningful Laboratory Values, Vital Signs, Physical Examinations and Other Observations Related to Safety

Any listings of information presented in this section of the 'primary use CSR' for regulatory review should fully support the review process. Listings data presented in this section in the 'secondary use CSR' for public disclosure should conform to **current** minimum standards for de-identifying data through piecemeal redaction, or may be fully redacted, depending on current requirements of the region.

14.4 OTHER DATA

Other data, for example, PD (which may include biomarkers), pharmacogenomics, quality of life and pharmacoeconomic endpoints data etc. may be presented.

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Comment [A559]: The ICH E3 section title is: 'Abnormal Laboratory Value Listing (Each Patient)'.
Clarification that these listings should capture only clinically meaningful abnormal values to avoid it becoming a data dump with little value.

Abnormal clinically meaningful vital signs and ECG data may also be listed because capture of "interesting" safety data should not be limited to laboratory data only. The section title should be adapted to reflect the listings actually presented.

Comment [A560]: Consider for PPD impact:
March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 87 of 91 states:
'EMA notes that under ICH E3, the CSRs may contain individual patient data listings … even within the body of the report. For example, these … may be contained in CSR section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit), as well as elsewhere in the CSR body … EMA considers that such per patient/per visit line listings fall outside the scope of phase 1 of the Policy [0070] and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy.'
Per page 6 of 91, Policy 0070 is in two phases. Phase 1 (01 January 20 pertains to publication of CSRs only. Phase 2, which will be implemented at a later stage, pertains to the publishing of individual patient data.

Comment [A561]: Consider for PPD impact:
Any 'other' data should be integrated into the end of text tables and figures section as is most appropriate to the study. Placement here is only an example.

Consider for PPD impact:
March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 87 of 91 states:
'EMA notes that under ICH E3, the CSRs may contain individual patient data listings … even within the body of the report. For example, these … may be contained in CSR section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit), as well as elsewhere in the CSR body … EMA considers that such per patient/per visit line listings fall outside the scope of phase 1 of the Policy [0070] and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy.'
Per page 6 of 91, Policy 0070 is in two phases. Phase 1 (01 January 20 pertains to publication of CSRs only. Phase 2, which will be implemented at a later stage, pertains to the publishing of individual patient data.

'Other data' may fall into the category described above and therefore the same rules may be applied by EMA.

15. REFERENCE LIST

A list of articles from the literature pertinent to the evaluation of the study, and cited in the CSR text, should be provided below. These may include conference abstracts and posters based on the study, as well as papers. Copies of important references may be attached in Appendices 16.1.11 and 16.1.12. All publications must be available and with the Sponsor at the time of filing of the submission.

Web addresses and digital object identifiers (DOIs) should be provided where possible. References should be given in accordance with the internationally accepted standards of International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References: http://www.nlm.nih.gov/bsd/uniform_requirements.html.

16. APPENDICES

This section should be prefaced by a full list of all appendices available for the study report. It is also acceptable to have the list of appendices integrated into the report table of contents. Where permitted by the regulatory authority, some of the following appendices need not be submitted with the report but need to be provided only on request.

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Comment [A562]: CORE Reference is a user manual and is not a template. The example sectioning and sub-sectioning is just that – an example.
The Reference List may sit equally well before Section 14 Tables, to directly follow the main CSR text.
The practical implications of switching the order of level 1 ICH E3 section headings in CORE Reference – here a Section 15 and Section 14 switch – are too far-reaching in terms of other external documents (including industry guidance documents) to make the switch within CORE Reference anything other than confounding.

Comment [A563]: Clarification that conference abstracts and posters may be included.

Comment [A564]: ICH E3 word 'publications' is substituted with 'references' here.

Comment [A565]: A cross link may be added in Appendix 16.1.11 and Appendix 16.1.12 to Section 15 (Reference List) as appropriate.

Comment [A566]: ICH E3 states that copies should be attached. However, guidance on inclusion of appendices for (European) MAA submissions clearly states 'for pivotal trials where these represent study end-points and otherwise on request'. This is also the case for FDA. In some regions, references may need to be attached with each CSR in 16.1.11 and 16.1.12. These appendices therefore need only be included and populated as appropriate.

Comment [A567]: Web addresses and digital object identifiers (DOIs):
Do not use active web links in the 'primary use CSR' for regulatory submission – just non active web addresses. This is because there is a risk of dossier validation problems when the CSR is submitted, sometimes years later.

The web addresses can subsequently be active in the 'secondary use CSR' for public disclosure.

Comment [A568]: ICH E3 mentions '… 1979 Vancouver Declaration on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" or the system used in "Chemical Abstracts".'
These older standards have been superseded by the International Committee of Medical Journal Editors (ICMJE) guideline cited here.

Comment [A569]: Such an example list is included in the following pages.

The Sponsor should therefore clearly indicate those appendices that are submitted with the report. Optimal documentary requirements are tabulated below.

Additional appendices may be created if the study necessitates this.

Note: In order to have appendices available on request, they should be finalised by the time of filing of the submission.

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Comment [A570]: See ICH E3 2012 Q & A Point 3 for CSR appendices: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf which states '*Documentation needed to review the CSR should be included in the CSR appendices. It is not sufficient for such documents to be included only in the TMF, which is not submitted in the marketing application. Documents that provide critical information on a study, such as the protocol (16.1.1), statistical methods (16.1.9), list of investigators and study sites and sample case report forms, would always be needed by reviewers assessing a study and should be included in the trial report even if they are in a TMF.*'
These are integrated into the table below.

Comment [A571]: Suggest to include a table for the list of appendices, with details.

Comment [A572]: There are certain requirements, especially in Appendix 16.1 Study Information, for MAA validation and for FDA (especially for studies do not come under an Investigational New Drug [IND] programme) that are not described in ICH E3, but are actually required. These are detailed in 'EMA pre-authorisation procedural advice for users of the centralised procedure'. 31 Mar 2016 EMA/339324/2007: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf
Relevant section for CSR appendices is '32. How are initial MAAs validated at the EMA: 'How to avoid most common GCP validation issues'. The points listed in this document are transcribed below for information. Disregard for non EU studies.

Comment [A573]: Consider for PPD and CCI impact: In the EU, CSR Appendices 16.1.1, 16.1.2 and 16.1.9 will be publicly disclosed (EMA Policy 0070 effective 1 Jan 2015: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf). and March 2016 EMA guidance on use of Policy 0070 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf) page 88 of 91: 'To be noted that the same CCI, PPD and publication principles will apply to EU as well as non-EU studies in the context of Policy 0070'.
See Preface for further detail on CCI, PPD and related topics.

Comment [A574]: See FDA Guidance on FDA Acceptance of Foreign Clinical Studies not Conducted Under an IND – Frequently Asked Questions: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf
Additional appendix requirements may be necessary e.g. Investigator CVs, and action dates of IRB/IEC approvals (e.g. initial approval date, date of approval of study amendments/modifications), master ICF. Suggest to collect the PI signature as a separate document submitted in MAA dossiers. This separates signature collections from CSR publishing, which may bring efficiencies when timelines are tight.

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Supportive documents, such as Investigator CVs, ethics committee approvals, informed consent forms, and batch numbers per subject are in the TMF or clinical supply database and should generally not be included in the CSR appendices.

Any documents not submitted and subsequently requested by the regulatory authority would be expected to be provided promptly.

Comment [A575]: ICH E3 2012 Q & A Point 3.

Appendix number	Content	Provide in appendix	To be available on request
16.1	Study Information		
16.1.1	Protocol and protocol amendments [Need not be signed copies; amended protocol versions subsequent to the original protocol are acceptable in place of actual protocol amendments, if available]	Yes	No
16.1.2	Sample case report form (may include unique pages only) [Including sample subject diary card or equivalent data collection tools]	Yes	No
16.1.3	List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) <Deliberate wider line spacing below to allow optimal presentation of ICH E3 2012 Q&A text> [*PIS/ICFs master versions and IEC/IRB approvals are in the TMF and are not required in Appendix 16.1.3*]	Yes (list only) No	Yes (IEC/IRB approvals) NA

Comment [A576]: i.e. in Sponsor's files.

Comment [A577]: Consider for CCI and PPD impact: In the EU, Appendix 16.1.1 will be publicly disclosed, so information included in this appendix may be redacted for the 'secondary use CSR' for public disclosure.

Comment [A578]: ICH E3 requirement of 'Representative written information for patient and sample consent forms' is omitted due to the ICH E3 2012 Q & A clarification Point 3.

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Appendix number	Content	Provide in appendix	To be available on request
16.1.4	List and description of Investigators and other important participants in the study [By-centre list of Investigators should show linkage of centres to the number of subjects enrolled and their IDs. 'Other important participants' including the CSR author and biostatistician may be included but need not be limited to individuals affiliated to CROs, central laboratories and other relevant specialist service providers] <Deliberate wider line spacing below to allow optimal presentation of ICH E3 2012 Q&A text> [*CVs are in the TMF and are not required in Appendix 16.1.4*]	Yes (list only)	Yes (CVs)

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Comment [A579]: i.e. in Sponsor's files.

Comment [A580]: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003638.pdf
Note for guidance on inclusion of appendices for MAA submissions clearly states under '16.3 CRFs' that 'the tabulation should enable the name and address of each Investigator and the number of subjects recruited by each site to be clearly linked'. This also applies for New Drug Applications (NDAs).

Comment [A581]: 'EMA pre-authorisation procedural advice for users of the centralised procedure'. 31 Mar 2016 EMA/339324/2007: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf
See 32. How are initial MAAs validated at the EMA: 'How to avoid most common GCP validation issues'. Information to be included in Appendix 16.1.4:

- **Ensure the list of Investigators (name, address, country), preferably in a tabular form, showing the number of patients enrolled by each site, and the total number of sites is included.**
- **Please make sure that a table with the number of patients enrolled per country is included. These should be identified in the CSR of each study, for instance in Section 10.1 or Appendix 16.1.4.**
- **Please make sure that a clear description of the study administrative structure (clear identification of the Sponsor and of the parties who have performed the monitoring, data management, statistics, laboratory assessments, randomization, site(s) of manufacture, other applicable activities and the location of the trial master file) preferably in a tabular form and indicating name and address of the site where each activity was performed, responsibilities and scope of each activity is included. These should be identified in the clinical study report of each study, for instance in Section 6, or Appendix 16.1.4.**

Consider for PPD impact: CORE Reference suggests placement of all this information in Appendix 16.1.4 and not in the main CSR text to simplify redaction in the 'secondary use CSR' for public disclosure. Disregard for non EU studies.

Comment [A582]: ICH E3 requirement of 'CVs' is omitted due to the ICH E3 2012 Q & A clarification Point 3.

Appendix number	Content	Provide in appendix	To be available on request
16.1.5	Signatures of Principal (for single-centre studies) or Coordinating Investigator(s) (for multi-centre studies) and/or Sponsor's responsible medical officer (depending on the Regulatory Authority's requirement) and signature of responsible biostatistician	Yes	No
16.1.6	List of Investigational Products(s) batch numbers [Per subject batch number linkage is in the clinical supply database and or TMF and is not required in Appendix 16.1.6]	Yes (list only)	Yes (batch numbers linked to subject numbers)
16.1.7	Randomisation scheme and codes (subject identification and treatment assigned)	Yes	No
16.1.8	Audit certificates (if necessary [region and/or country-specific], and if available)	Yes	No

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Comment [A583]: i.e. in Sponsor's files.

Comment [A584]: Addition of 'and/' to ICH E3 text is to clarify that all regions per ICH E3 require the Principal or Coordinating Investigator signature OR the Sponsor's responsible medical officer signature. Historically and globally, the medical officer signature became the standard choice.
Later, in 2001, the EMEA issued its Note for Guidance on Coordinating Investigator signature of CSRs: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003656.pdf which states 'CSRs submitted as part of Marketing Authorisation Application... should be signed by the Investigator or in the case of multicentre studies the Coordinating Investigator… the signatory Coordinating Investigator should be defined in the protocol…'.
The final outcome is that in all regions, the Sponsor's responsible medical officer should sign the CSR. In the EU, the Investigator should additionally sign (EU Sponsors are unlikely to have the Investigator but not their own medical officer sign, which is why both signatures are usually required for EU studies).
Also see CORE Reference Annex I.

Comment [A585]: See ICH E9 Statistical Principles for Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
Section 7.1 final paragraph which states: '...the trial statistician should be a member of the team responsible for the clinical study report, and should approve the clinical report.' Also see CORE Reference Annex I.

Comment [A586]: ICH E3 requirement of subject batch number linkage is omitted due to the ICH E3 2012 Q & A clarification Point 3: '*Supportive documents, such as investigator CVs, ethics committee approvals, informed consent forms, and batch numbers per subject are in the TMF or clinical supply database and should generally not be included in the CSR appendices*'. 'Investigational Product' includes Test Product and Control Product which may include placebo or active comparator. For terminology related to Investigational Product see Preface.

Comment [A587]: Include internal or external auditing procedures if used. Do not include audit reports.

Comment [A588]: Clarification that regional and country-specific requirements must be adhered to.

Comment [A589]: Per ICH E3 2012 Q & A Point 3: '*Certain documents may be required for the CSR by individual countries or regions, in which case they should be included. For example, according to ICH-GCP, an audit certificate (16.1.8) should be provided when required by applicable law or regulation. If there is any uncertainty about whether documents should be included or not, the appropriate regulatory agency may be consulted.*'

Appendix number	Content	Provide in appendix	To be available on request
16.1.9	Documentation of statistical methods [Need not be a signed copy] [*Post-hoc* analyses (including *post-hoc* analysis methods and results if conducted and available by final CSR date) if not included in the main CSR text]	Yes Yes (if available by final CSR date)	No Yes (if not available by final CSR date)
16.1.10	Documentation of inter-laboratory standardisation methods and laboratory QA procedures if used (depending on the Regulatory Authority's requirement) [For pivotal studies where these represent study endpoints]	Yes – (pivotal studies only)	Yes (all non-pivotal studies)
16.1.11	Publications based on study	Preferred	Yes (actual publications)
16.1.12	Important publications referenced in the report	Preferred	Yes (actual publications)

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Comment [A590]: i.e. in Sponsor's files.

Comment [A591]: Clarification on signatures. There is no regulatory requirement for signature(s).

Comment [A592]: Clarification on *post-hoc* analyses.

Comment [A593]: Clarification that the included documentation of QA procedures should relate to laboratories.

Comment [A594]: Laboratory validation procedures and/or certificates, equipment calibration, internal QC or external QA procedures. No laboratory manuals required. Applies to central, local and specialist laboratories.

Comment [A595]: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003638.pdf
Guidance on inclusion of appendices for (European) MAA submissions clearly states 'for pivotal trials where these represent study end-points and otherwise on request'. This is also the case for NDAs.

Comment [A596]: In practice, this appendix may often be unpopulated. Cross check with the information provided in the Synopsis (which notes posters and abstracts should be included). Posters and abstracts are particularly hard to obtain years later so it is sensible to have them available at CSR finalisation.

Comment [A597]: Actual PDFs of references are required in Module 5 of a submission dossier.

Comment [A598]: Can be all of or a subset of the references listed in Section 15.

Comment [A599]: Consider that:
a). The CSR may be final many years before the dossier is submitted, and b). Only a small number of CSRs ever end up in a submission dossier.
In light of this, including the actual references in Appendices 16.1.11 and 16.1.12 may avoid possible complications subsequent to CSR finalisation.
NOTE: In practice, only one set of references are actually required in a regulatory dossier submission.

Comment [A600]: The intent of Appendices 16.1.11 and 16.1.12 is to gather actual references so they are 'available' at the time of CSR finalisation.

Comment [A601]: Actual PDFs of references are required in Module 5 of a submission dossier.

Appendix number	Content	Provide in appendix	To be available on request
16.1.13	Optional Appendix e.g. Data Monitoring Committee, <Deliberate wider line spacing below to allow optimal presentation of ICH E3 2012 Q&A text> *Stand-alone reports, e.g. PK report,* *PRO report*	Yes	No

Comment [A602]: i.e. in Sponsor's files.

Comment [A603]: If DMC materials are included, the DMC charter and key meeting minutes should suffice.

Comment [A604]: An additional appendix, for example, Appendix 16.1.13, is suggested for the inclusion of stand-alone reports, as appropriate.

Comment [A605]: ICH E3 2012 Q & A Point 4 encourages inclusion of relevant stand-alone reports, as necessary: '*Other topics should be well referenced in the CSR body and clearly identified in the Table of Contents. Current submission options include: 1) Stand alone reports. These can be placed in "parallel" with the main CSR in the eCTD. For example, a clinical pharmacology study might have the CSR, a PK report, and an assay validation report. For an efficacy study with patient reported outcome (PRO) measures, there might be a PRO report. Each of these reports can be referenced under the same heading in the eCTD and placed alongside one another in the eCTD folder for that study. Be sure to clearly describe the nature of the information in the title of the document that is provided through the eCTD. 2). In a region where study tagging files are used. It is recommended that a file tag option from the "valid values list" be used, for example, safety report, antibacterial, special-pathogen, etc. (see Specifications for Study Tagging Files, http://www.ich.org/products/electronic-standards.html). Alternatively, if a file-tag that adequately describes the material you are planning to submit is not available, you may request that a new file-tag be made available. This request should be submitted to your regional authority. In the event that this change cannot be accommodated within your timeframe you may place the document with the main body of the report, i.e., the document would be tagged with the "study-report-body" file-tag. The nature of the information should be contained in the title of the document that is provided through the eCTD. Please refer to the most recent version of the "valid values list", as it is periodically updated as changes are requested.*'

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ICH E3 text *ICH E3 2012 Q&A text* CORE Reference text [Right margin comment=RATIONALE]

Appendix number	Content	Provide in appendix	To be available on request
16.2	Subject Data Listings 16.2.1 Discontinued Subjects 16.2.2 Protocol Deviations 16.2.3 Subjects Excluded from the Efficacy Analysis 16.2.4 Demographic Data 16.2.5 Compliance and/or Drug Concentration Data (if available) 16.2.6 Individual Efficacy Response Data 16.2.7 Adverse Events Listings (each Subject) 16.2.8 Listing of Individual Laboratory Measurements by Subject When Required by Regulatory Authorities	Yes	No
16.3	Case Report Forms 16.3.1 CRFs for deaths, other SAEs and withdrawals for AE 16.3.2 Other CRFs submitted (only if applicable)	Yes (for narrative subjects only Yes (if applicable)	Yes (all other CRFs) No
16.4	Individual Subject Data Listings (US archival listings)	No	No

Comment [A606]: i.e. in Sponsor's files.

Comment [A607]: See CORE Reference Annex IV text relevant to creation of Appendix 16.2 listings content, gathered together from various places in ICH E3 and presented below for the use, primarily, of statisticians.

Comment [A608]: For FDA submissions, Subject Data Listings need not necessarily be produced due to the common practice of submission of searchable SAS data sets to authorities. See FDA resources for data standards: http://www.fda.gov/ForIndustry/DataStandards/.

Comment [A609]: In practice, it seems CRFs are not always submitted and this depends on the study. Advice is to check with your regulatory agency/authority before filing.

Comment [A610]: US Archival Listings need not be produced due to the common practice of submission of searchable SAS data sets to authorities. See FDA resources for data standards: http://www.fda.gov/ForIndustry/DataStandards/.

Archival listings are not usually required by other regulatory authorities. This may however depend on the drug and therapeutic area. Confirmation from the respective regulatory authority is advised. Some regulatory authorities may require certain listings only (e.g. SAE).

Explanation of Annexes in ICH E3 and in CORE Reference

Annex number – Title (in ICH E3)	Position in CORE Reference
I – Synopsis	Example synopsis table is included in Section 2 (Synopsis) of CORE Reference (so Annex I Synopsis is removed from annexes)
II – Principal or Coordinating Investigator(s) Signature(s)	Renumbered Annex I and included below
IIIa – Study Design and Schedule of Assessments	Example Table 9.1 in CORE Reference is derived from Annexes IIIa and IIIb (which are therefore omitted from annexes)
IIIb – Study Design and Schedule of Assessments	
IVa – Disposition of Patients	Example Figure 10.1 in CORE Reference is derived and amended from Annexes IVa and IVb (which are therefore omitted from annexes)
IVb – Disposition of Patients	
V – Study # (Data Set Identification) Listing of Patients Who Discontinued Therapy	Renumbered Annex II and included below
VI – Study # (Data Set Identification) Listing of Patients and Observations Excluded From Efficacy Analysis	Renumbered Annex III and included below
VII – Study # (Data Set Identification) Number of Patients Excluded from Efficacy Analysis	Example Table 10.2 in CORE Reference is derived and amended from Annex VII (which is therefore omitted from annexes)
VIII – Guidance for Section 11.4.2 – Statistical/Analytical Issues and Appendix 16.1.9	Section 11.4.2 in the body of CORE Reference is now renumbered Section 11.2 (Results of Statistical Issues Encountered During The Analysis) Annex VIII is renumbered Annex IV and included below with text adaptations. Notes per ICH E3 Section 11.4.3 (Tabulation of Individual Response Data), and Section 12.4.1 (Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value), which are actually relevant to creation of Appendix 16.2 listings generally, are appended to this annex. These notes are more appropriately annexed than placed in the body of CORE Reference as are relevant to the statistician only
	Annex V is new and shows 'Adverse Events: Number Observed and Rate, with Subject Identifications'. This is in ICH E3 Section 12.2.2 (Display of Adverse Events) but does not appear in CSR text, but rather is usually appended, so is more appropriately relocated to new Annex V
	Annex VI is new and shows 'List of Laboratory Measurements'. This is in ICH E3 Section 12.4.1 (Listing of individual laboratory measurements by subject [16.2.8] and each abnormal laboratory value [14.3.4]) but does not appear in CSR text, but rather is usually appended, so is more appropriately relocated to new Annex VI, and is additionally redesigned more appropriately to two tables that might be used

Annex I (Appendix 16.1.5)

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) (AND/OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER SIGNATURE AND STATISTICIAN'S SIGNATURE)

STUDY TITLE:

STUDY NUMBER:

REPORT VERSION: Final (Date)

STUDY AUTHORS:

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

PRINCIPAL/COORDINATING INVESTIGATOR:

SIGNATURE:

AFFILIATON:

DATE:

SPONSOR'S RESPONSIBLE MEDICAL OFFICER:

SIGNATURE:

AFFILIATON:

DATE:

STATISTICIAN:

SIGNATURE:

AFFILIATON:

DATE:

Comment [A611]: Annex II in ICH E3.

Comment [A612]: Addition of 'and/' to ICH E3 text is to clarify that all regions per ICH E3 require the Principal or Coordinating Investigator signature OR the Sponsor's responsible medical officer signature. Historically and globally, the medical officer signature became the standard choice.
Later, in 2001, the EMEA issued its Note for Guidance on Coordinating Investigator signature of CSRs: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003656.pdf which states 'CSRs submitted as part of Marketing Authorisation Application... should be signed by the Investigator or in the case of multicentre studies the Coordinating Investigator… the signatory Coordinating Investigator should be defined in the protocol…'.
The final outcome is that in all regions, the Sponsor's responsible medical officer should sign the CSR. In the EU, the Investigator should additionally sign (EU Sponsors are unlikely to have the Investigator but not their own medical officer sign, which is why both signatures are collected as standard for EU studies).

Comment [A613]: See ICH E9 Statistical Principles for Clinical Trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
Section 7.1 final paragraph which states: '...the trial statistician should be a member of the team responsible for the clinical study report, and should approve the clinical report.'

Comment [A614]: ICH E3 States in Section 6: 'Where signatures of the Principal or Coordinating Investigators are required by regulatory authorities, these should be included in Appendix 16.1.5 Where these are not required, the signature of the Sponsor's responsible medical officer should be provided in Appendix 16.1.5.'

For EU studies only, include Principal/Coordinating Investigator signature as well as Sponsor's medical officer signature. Omit if not applicable.

Comment [A615]: Added per ICH E9 requirement.

Annex II (Appendix 16.2.1)
Listing of Subjects Who Discontinued Treatment (Data Set Identification)

Centre:

Investigational Product	Reason for Discontinuation	Subject Identifier	Sex	Age	Day of Last Visit	Day of Last Dose	Duration of Treatment (days)	Dose (unit) at Time of Discontinuation	Concomitant Medication
Test Product	Adverse Event: *insert details if captured* Treatment failure								
Control Product (may include active comparator or placebo)									

Day is relative to first dose of Investigational Product.
Data source: xxx
(Repeat for other centres)

Comment [A616]: ICH E3 Annex V.

Comment [A617]: Content is essentially the same as ICH E3 Annex V, with adapted presentation.

Comment [A618]: Terminology around Investigational Product is aligned with terminology in the CORE Reference Preface.

Comment [A619]: This is a listing and will not appear in this form in the CSR text. It is expected that the protocol number will appear in the data source of all statistical output. This aids regulators who may copy these into their own documents. Output without a study number (included as part of the source) may cause confusion.

Annex III (Appendix 16.2.3)
Listing of Subjects and Observations Excluded from the Efficacy Analysis

Centre:

Investigational Product	Subject Number	Sex	Age	Observation Resulting in Exclusion	Reason(s) for Exclusion
Test Product					
Control Product (may include active comparator or placebo)					

Data source: xxx
(Repeat for other centres)

Comment [A620]: ICH E3 Annex VI.

Comment [A621]: Content is essentially the same as ICH E3 Annex VI, with adapted presentation.

Comment [A622]: Terminology around Investigational Product is aligned with terminology in the CORE Reference Preface.

Comment [A623]: This is a listing and will not appear in this form in the CSR text. It is expected that the protocol number will appear in the data source of all statistical output. This aids regulators who may copy these into their own documents. Output without a study number (included as part of the source) may cause confusion.

Annex IV

GUIDANCE FOR SECTIONS 9.7 AND 11.2 – STATISTICAL ISSUES AND APPENDIX 16.1.9

A. STATISTICAL CONSIDERATIONS

Details of the statistical analysis performed on each efficacy variable should be presented in an appendix. Details reported should include at least the following information:

a) A statement of the clinical claim tested in precise statistical terms, e.g. in terms of null and alternative hypotheses.

b) The statistical model underlying the analysis. This should be presented precisely and completely, using references if necessary. If any model fitting was performed, this should be described noting all terms included in the original model, any terms removed because they were not statistically significant and the terms fitted in the final model. The method of model fitting as specified in the final SAP (e.g. stepwise regression with backward elimination) should be stated. Model fitting should only be performed if planned in the final SAP. The risk of bias introduced by making unplanned changes to the model should be clearly stated.

c) The assumptions underlying the planned statistical methods. It should be shown, insofar as statistically reasonable, that the data satisfy crucial assumptions, especially when necessary to confirm the validity of an inference. In the event that the assumptions are not met, then the alternative methods should be detailed. These may include:

(i) Transformation of the data such that the assumptions of the planned model are met.

(ii) Performing an alternative analysis where the data do meet the assumptions.

Any alternative methods should be detailed in addition to details of the originally planned analysis method. It should be clearly stated whether the alternative approaches were planned (stated as an alternative in the final SAP) or whether the decision to use alternative methods was taken after study unblinding. The risk of bias introduced by selecting alternative methods post-unblinding should be clearly stated.

d) The statistical methods applied to estimate effects, construct confidence intervals, etc. Literature references should be included where appropriate. If data have been transformed prior to analysis, then it should also be stated how to interpret treatment effects.

e) The test statistic, the sampling distribution of the test statistic under the null hypothesis, the value of the test statistic, significance level (i.e. p-value) and intermediate summary data, in a format that enables the regulatory authority's statistical reviewer to verify the results of the analysis quickly and easily. The p-values should be designated as one- or two-tailed. The rationale for using a one-tailed test should be provided.

For example, the documentation of a two-sample t-test should consist of the value of the t-statistic, the associated degrees of freedom, the p-value, the two sample sizes, mean and variance for each of the samples and the pooled estimate of variance. The documentation of multi-centre studies analysed by variance techniques should include, at a minimum, an analysis of variance table with terms for centres, treatments, their interaction, error and total. For crossover designs, the documentation should include information regarding

Comment [A624]: ICH E3 Annex VIII.

Comment [A625]: This Annex provides detailed supplemental information to Section 9.7 and is therefore not integrated with Section 9.7.

Comment [A626]: ICH E3 term 'statistical/analytical' is substituted with 'statistical' only.

Comment [A627]: Omission of 'primary'.

Comment [A628]: The points listed in this section should ensure transparency of methods used and timing of decisions such that the regulatory authority reviewer can draw that conclusion anyway. Thus, text has been updated to omit the statement that implies that it may be acceptable to present statistical conclusions based on results with questionable validity. The reporting statisticians should be encouraged to pre-plan and perform the analyses in line with decisions taken prior to unblinding and taking all necessary measures to limit the introduction of bias.

Comment [A629]: ICH E3 point d) (i) states that 'in the event data transformation was performed, a rationale for this choice … should be provided'. This requirement for a rationale for the choice of data transformation has been omitted. The data transformation is being performed because the assumptions of the original statistical model were not met and so that is the rationale.

Comment [A630]: ICH E3 point d) states that 'any subgroup analyses that are not preplanned will ordinarily not provide an adequate basis for definitive conclusions'. This statement has been omitted because analyses that are not preplanned will not provide an adequate basis for definitive conclusion regardless of what those analyses are. It is misleading to single out subgroup analyses, as it suggests that other *post-hoc* analyses might introduce less bias. Revisions to points b) and c) now cover risk of bias from unplanned changes to the model, using unplanned alternative models or making unplanned transformations to the data.

Comment [A631]: The ICH E3 text: 'd) (ii) A discussion of the appropriateness of the choice of statistical procedure and the validity of statistical conclusions will guide the regulatory authority's statistical reviewer in determining whether reanalysis of data is needed' is omitted because emphasis has already been placed on documenting the choice of statistical procedures that would lead to valid statistical conclusions. Discussion of already implemented procedures is not encouraged.

sequences, subjects within sequences, baselines at the start of each period, washouts and length of washouts, dropouts during each period, treatments, periods, treatment by period interaction error and total. For each source of variation, aside from the total, the table should contain the degrees of freedom, the sum of squares, the mean square, the appropriate F-test, the p-value and the expected mean square.

Intermediate summary data should include the demographic data and response data, averaged or otherwise summarised, for each centre-by-treatment combination (or other design characteristic such as sequence) at each observation time.

Comment [A632]: The following ICH E3 text is omitted as is outdated. The only agency (FDA) who actually does do such a thorough review receives SAS transport files:
'B. FORMAT AND SPECIFICATIONS FOR SUBMISSION OF DATA REQUESTED BY REGULATORY AUTHORITY'S STATISTICAL REVIEWERS

In the report of each controlled clinical study, there should be data listings (tabulations) of patient data utilised by the Sponsor for statistical analyses and tables supporting conclusions and major findings. These data listings are necessary for the regulatory authority's statistical review and the Sponsor may be asked to supply these subject data listings in a computer-readable form.'

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B. GUIDANCE FOR APPENDIX 16.2 LISTINGS – GENERAL NOTES:

For a controlled study in which critical measurements or assessments (e.g. blood or urine cultures, pulmonary function tests, angina frequency or global evaluations) are repeated at intervals, the data listings accompanying the report should include, for each subject, a subject identifier, all measured or observed values of critical measurements, including baseline measurements, with notation of the timing during the study expressed relative to a fixed point (e.g. day relative to first dose of Investigational Product, and time of day if relevant) when the measurements were made, the drug/dose at the time (if useful, given as mg/kg), any measurements of compliance and any concomitant medications at the time of, or close to the time of, measurement or assessment. If, aside from repeated assessments, the study included some overall responder versus non-responder evaluation(s) (bacteriologic cure or failure), these should also be included. In addition to critical measurements, the tabulation should note whether the subject was included in the efficacy evaluation (and which evaluation, if more than one), provide subject compliance information (if collected) and a reference to the location of the CRF, if included. Critical baseline information such as age, sex, weight, disease being treated (if more than one in the study) and disease stage or severity, is also helpful. The baseline values for critical measurements would ordinarily be included as zero time values for each efficacy measurement.

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Comment [A633]: In ICH E3, details pertaining to listings creation in Section 11.4.3 (Tabulation of Individual Response Data) are applicable more generally to all data listings presentations. The content is of relevance for statisticians and is presented here for clarity.

Comment [A634]: ICH E3 Section 11.4.3 text first paragraph is omitted because the FDA is the only agency who has previously requested this and now they receive SAS transport files – so this belongs to a bygone era:
ICH E3 text omitted: 'Some regulatory authorities may require all individual data in archival case report tabulations. What needs to be included in the report will vary from study to study and from one drug class to another and the Sponsor must decide, if possible after consultation with the regulatory authority, what to include in the appendix to the study report. The study report should indicate the material that is included as an appendix; the more extensive archival case report tabulations, if required by the regulatory authority, and what is available on request.'.

Comment [A635]: The word 'efficacy' is omitted.

Comment [A636]: Consider for PPD impact: ICH E3 text specifies that subject identifiers should be present on listings. Subject numbers may be created using a centre identifier component. Subject re-identification, particularly for centres entering small numbers of study subjects, may be possible through a subject number that includes a centre identifier component. Where individual subject numbers are presented in the 'primary use CSR', it is recommended that these are fully redacted in the 'secondary use CSR' for public disclosure. In all cases, the entire subject number - including any centre identifier component – should be redacted.

Comment [A637]: Consider for PPD impact: Calendar dates would not be allowed in the 'secondary use CSR' for public disclosure as these may increase the chance of subject re-identification. In the 'primary use CSR' for regulatory review, only refer to study days and do not refer to calendar dates. This approach captures event timing (necessary to inform the assessment of temporal association) in the 'primary use CSR' without increasing redaction need in the 'secondary use CSR'.

Note however, that this may need special consideration for some illnesses where dates can be important, for example, allergy and seasonal affective disorder where alternative presentations should be considered that still avoid the actual date.

Comment [A638]: ICH E3 text: '(e.g., days on therapy)' is clarified.

The listings described should usually be included in Appendix 16.2 of the study report, rather than in the more extensive case report tabulations required by some regulatory authorities, because it represents the basic data supporting the summary tables. However, such a thorough tabulation can be unwieldy for review purposes and it is expected that more targeted displays will be developed as well. For example, if there are many measurements reported, tabulations of the most critical measurements for each subject (e.g. the blood pressure value might be more important at certain visits than others) will be useful in providing an overview of each individual's results in a study, with each subject's response summarised on a single line or small number of lines.

While individual subject data ordinarily can be displayed in listings, it has, on occasion, been helpful to construct individual subject profiles in other formats, such as graphic displays. These might, for example, show the value of a particular parameter(s) over time, the drug dose over the same period and the times of particular events (e.g. an AE or change in concomitant treatment). Where group mean data represent the principal analyses, this kind of "case report extract" may offer little advantage; it may be helpful, however, if overall evaluation of individual responses is a critical part of the analysis. If such profiles are presented, these should be cross-referenced in the CSR text.

C. GUIDANCE FOR APPENDIX 16.2 LISTINGS – LABORATORY DATA:

When required by regulatory authorities, the results of all safety-related laboratory tests should be available in listings, using a display where each row represents a patient visit at which a laboratory study was done, with patients grouped by investigator (if more than one) and treatment group, and columns include critical demographic data, drug dose data, and the results of the laboratory tests, similar to the example in Annex VI. As not all tests can be displayed in a single table, they should be grouped logically (haematological tests, liver chemistries, electrolytes, urinalysis, etc.). In addition, normal laboratory ranges should be given for each laboratory parameter.

Abnormal values should be identified and graded according to an established toxicity grading scale, or designated clinically meaningful or not clinically meaningful, according to the Investigator's judgment at the time the result became available. These listings should be submitted as part of the registration/marketing application, when this is required, or may be available on request. Examples of such listings are presented in Annex VI.

For all regulatory authorities, there should be a by-subject listing of all abnormal laboratory values presented in Section 14.3.4 (Data Listings [Each Subject] for Abnormal Clinically Meaningful Laboratory Values, Vital Signs, Physical Examinations and Other Observations Related to Safety), using the formats described above.

For laboratory abnormalities of special interest (abnormal laboratory values of potential clinical importance), it may also be useful to provide additional data, such as normal values before and after the abnormal value, and values of related laboratory tests. In some cases, it may be desirable to exclude certain abnormal values from further analysis. For example, single, non-replicated, small abnormalities of some tests (e.g. uric acid or electrolytes) or occasional low values of some tests (e.g. transaminase, alkaline phosphatase, BUN etc.) can probably be defined as not clinically meaningful and excluded. Any such decisions should be clearly explained, however, and the complete list

Comment [A639]: Text clarified with no loss of meaning.

Comment [A640]: Omission of 'tabular'.

Comment [A641]: Consider for PPD impact: In the event that subject numbers are transcribed into the CSR text, subject numbers with no centre-identifier component will reduce the risk of identifying subjects and therefore minimise the need for piecemeal redaction in the 'secondary use CSR' for public disclosure.

Comment [A642]: ICH E3 Section 11.4.6 text (By-patient Displays) is relocated here.

Comment [A643]: Details pertaining to listings creation in ICH E3 Section 12.4.1 (Listings of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value) are actually of relevance for statisticians and are presented here for clarity.

Comment [A644]: Omission of 'tabular'.

Comment [A645]: ICH E3 describes a display: 'similar to the following'. This text is omitted, because reference to Annex VI is subordinated in the sentence instead.

Comment [A646]: The Annex VI example listing is added for clarity.

Comment [A647]: ICH E3 Section 12.4.2 (Evaluation of Each Laboratory Parameter) text 'In addition, normal laboratory ranges should be given for each analysis.' has been amended (as it is not possible to ascribe normal ranges for analyses – i.e. summary laboratory data. Normal ranges can only ever apply to individual laboratory parameters and be compared with each subject's results). The resulting revised text is relocated here.

Comment [A648]: ICH E3 suggests '…by underlining, bracketing etc.'.

Comment [A649]: Clarification to state that abnormal values should be identified, and designated clinically meaningful (CM) or not clinically meaningful (NCM), according to the Investigator's judgement – where an established toxicity grading scale is not used. Alternative terminology, e.g. 'clinically significant' or 'not clinically significant' is often used. Use language appropriate for the study.

Comment [A650]: All abnormal laboratory values need not always be included for all studies, e.g. if this would result in a rather lengthy listing. It also depends on the drug and development programme and therapeutic area. Abnormal laboratory values also may be rare in certain disease areas. Given these insights, the listing should list what is appropriate.

of values provided (or available to authorities on request) should identify every abnormal value.

Annex V (Appendix 16.2.7)

Adverse Events: Number Observed and Rate, With Subject Identifications

	Treatment Group X, N=50								
	Mild		Moderate		Severe		Total		Total
	Related*	NR	Related*	NR	Related*	NR	Related*	NR	R+NR
Body System A									
Event 1	6 (12%)	2 (4%)	3(6%)	1 (2%)	3 (6%)	1 (2%)	12 (24%)	4 (8%)	
	N11**	N21	N31	N41	N51	N61			
	N12	N22	N32		N52				
	N13		N33		N53				
	N14								
	N15								
	N16								
Event 2									

NR = not related.
* Related could be expanded, e.g. as definite, probable, possible
** Subject identification number
Data source: xxx

Comment [A651]: This table is in ICH E3 Section 12.2.2. It is annexed per ICH E3 2012 Q & A Point 6 (see below). This also avoids inclusion of the subject IDs in the main CSR in-text table.

The ICH E3 Section 12.2.2 text suggests that the regulatory authorities are interested in the subject numbers.

Comment [A652]: ICH E3 2012 Q & A Point 6 states: '*Of note, the example table provided in Section 12.2.2 of the Guideline is not meant to be presented in Section 12.2.2 of the report, but in Section 14.3.1, which is not part of the text of the clinical study report.*

The ICH E3 Guideline did not attempt to display all possible presentations of adverse event information, but rather outlined the summary table intended for Section 12.2.2 and provided an illustration of the far more detailed display that would be placed in Section 14.3.1. The example provided for Section 14.3.1, however, does not try to illustrate all possibilities, but shows individuals with adverse events by body system, severity, and perceived drug-relatedness, for treatment group "X".

Listings should also display investigator's verbatim terms for each event and could be used to show demographic or disease-specific information, dosage, duration of treatment, or treatment cycle (for cancer chemotherapy). Because it can be impractical to display all of this information in a single listing, such analyses can be presented in individual listings, e.g., by dose or other subgroup of interest. When adverse event data are presented by subgroup, however, a display of overall adverse events should also be included. For example, for a drug for subjects with chronic kidney disease, adverse events could be tabulated separately for subjects receiving or not receiving dialysis, but a table that includes adverse events in all subjects should also be included. The listings that provide more comprehensive adverse event information, specifically subject identifiers and verbatim terms for each adverse event, should be provided in the study report, in Sections 14.3.1 and 16.2.7. If each adverse event is to be characterized extensively (i.e., many items in the listing), electronic approaches may be needed.'

Comment [A653]: This is a listing and will not appear in this form in the CSR text. It is expected that the protocol number will appear in the data source of all statistical output. This aids regulators who may copy these into their own documents. Output without a study number (included as part of the source) may cause confusion.

Annex VI (all measurements in Listing 16.2.8; abnormal measurements in Listing 14.3.3)

Listing of Laboratory Measurements

Subject number and demographic data	Days on treatment	Dose	Test parameter (unit)	Reference range	Test result	Toxicity grade

Footnote to describe toxicity grading scale
Data source: xxx

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ICH E3 text *ICH E3 2012 Q&A text* CORE Reference text [Right margin comment=RATIONALE]

Comment [A654]: ICH E3 'Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)' is adapted to more accurately reflect the content of both listings.

The basis for these suggested tables is ICH E3 Section 12.4.1 'List of laboratory measurements' – tabular presentation *in situ* with ICH E3 text. Consider for PPD impact: The tabulations presented below include demographic data per the ICH E3 tabulation. Consider that data transcribed from these tables into the 'primary use CSR' text may require redaction in the 'secondary use CSR' for public disclosure.

Comment [A655]: ICH E3 Section 12.4.1 describes a display: '… where each row represents a patient visit at which a laboratory study was done, with patients grouped by investigator (if more than one) and treatment group, and columns include critical demographic data, drug dose data, and the results of the laboratory tests.'
These tables are designed accordingly.

Comment [A656]: Consider for PPD impact: The data included in this (or any similar) listings will necessitate careful consideration when transcribing data into the CSR. Data included in the 'primary use CSR' for regulatory review must be sufficient to support the review and may need to be redacted in the 'secondary use CSR' for public disclosure to protect subject anonymity.

Comment [A658]: Timepoints may be shown.

Comment [A657]: Demographic data may include age, sex, race, weight etc.

Comment [A659]: This is a listing and will not appear in this form in the CSR text. It is expected that the protocol number will appear in the data source of all statistical output. This aids regulators who may copy these into their own documents. Output without a study number (included as part of the source) may cause confusion.

OR:

Listing of Laboratory Measurements

Subject number and demographic data	Days on treatment	Dose	Test parameter (unit)	Reference range	Test result	Abnormal (No/Yes)	Clinical meaning for abnormal results only (CM/NCM)

CM, clinically meaningful; NCM, not clinically meaningful
Data source: xxx

Comment [A660]: Consider for PPD impact: The data included in this (or any similar) listing will necessitate careful consideration when transcribing data into the CSR. Data included in the 'primary use CSR' for regulatory review must be sufficient to support the review and may need to be redacted in the 'secondary use CSR' for public disclosure to protect subject anonymity.

Comment [A662]: Timepoints may be shown.

Comment [A661]: Demographic data may include age, sex, race, weight etc.

Comment [A663]: The terms 'clinically significant' and 'not clinically significant' are also widely used.

Comment [A664]: This is a listing and will not appear in this form in the CSR text. It is expected that the protocol number will appear in the data source of all statistical output. This aids regulators who may copy these into their own documents. Output without a study number (included as part of the source) may cause confusion.

LIST OF ABBREVIATIONS USED IN CORE REFERENCE

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CCI	Commercially Confidential Information
CDER	(FDA) Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CI	Coordinating Investigator
CIOMS	Council for International Organisations of Medical Sciences
Cmax	Maximum Plasma Concentration
CORE	Clarity and Openness in Reporting: E3 based
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Regulation
CV	Curriculum Vitae
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DoH	Declaration of Helsinki
DOI	Digital Object Identifier
EC	Ethics Committee
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials (Database)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
NCI	National Cancer Institute
NDA	New Drug Application
NEJM	New England Journal of Medicine
NIH	National Institutes of Health
PD	Pharmacodynamic(s)
PET	Positron Emission Tomography
PhUSE	Pharmaceutical Users Software Exchange
PI	Principal Investigator
PIP	Paediatric Investigation Plan
PIS	Patient Information Sheet
PK	Pharmacokinetic(s)
PPD	Protected Personal Data
PRO	Patient Reported Outcome
QA	Quality Assurance
QC	Quality Control
Q & A	Questions & Answers
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRMO	Sponsor's Responsible Medical Officer
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, Listings
TMF	Trial Master File
ToC	Table of Contents