Effective authoring of clinical study reports: A companion guide

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Abstract

'*Why write a clinical study report (CSR)? What are the guidance documents? Can I interpret them? Can I deliver my CSR on time?*' This article addresses these questions – and others, provides a companion guide to CSR authoring for preregistration drug trials intended for regulatory submission in the EU, provides links to applicable regulatory guidance documents, and offers experience-based insights. Between 2008 and 2013, the authoring timeline for a medium complexity first draft (mean [SD]: 16.9 [8.2]; range: 5–45 working days) and final CSR from the first draft (mean [SD]: 25.7 [21.1]; range: 3–120 working days) varied widely across the industry. Understanding regulatory requirements and utilising project intelligence leads to informed CSR authoring and scheduling, thereby assuring a high-quality, on-time, final CSR.

Keywords: Clinical study report, Regulatory Guidance, ICH E3, ICH E6, Reporting

Reasons for writing a clinical study report

The regulatory and ethical basis for writing clinical study reports (CSRs) is grounded in Section 5.2.2 of the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6[1] (henceforth ICH E6):

> *Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s).*

ICH E6 further directs us to the ICH Guideline for Structure and Content of Clinical Study Reports[2] (henceforth ICH E3):

> *The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports.*

A summary of the results must be produced[1] within a year of the end of the trial.[3] It is expected that in the later part of 2014, online posting of summary results on the European Medicines Agency (EMA) European Clinical Trials (EudraCT) database will become mandatory.[4]

Although the ICH region includes the EU, Japan and the USA, this article focuses primarily on the preparation of full CSRs for regulatory submission in the EU prior to approval (henceforth Marketing Authorisation Application [MAA]). Preparation of abbreviated and synopsis CSRs are additionally covered in brief.

The target audience for a CSR is most often the regulatory reviewer. However, CSRs are not always intended to contribute to an MAA. A CSR may report a 'proof of concept' study and may be used to secure development funding, or pass on information to an acquisitor of a drug. Such studies may subsequently be redesigned and repeated with greater regulatory rigour if repurposed for an MAA. In addition, some of the data in MAAs (including CSRs), submitted to EMA from March 2014, will be made publicly accessible.[5] This means that requests can be made for access to CSRs and datasets, and that successful requesters can reanalyse the data.

Whatever the reason for writing a CSR, and whatever the breadth of audience, a well-structured and well-written document will support the development programme, submission process, and ultimately labelling, because this key regulatory document is the basic building block of the MAA. Immediate reporting on completion of the study is recommended, not only because of summary

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results public posting requirements,[1,3] but because the team's availability and recollection of study detail will most likely be optimal.

A 'fit for purpose' clinical study report

A 'fit for purpose' document fulfils reporting requirements and supports the work of the regulatory reviewer – a time-poor professional, often reviewing and comparing data across different MAAs. The regulatory reviewer will appreciate clarity, consistency, and brevity. They must be able to find information with ease. The CSR author is key in facilitating this process. Report version (draft or final) and date must be clearly displayed on the title page and on each page. A data cut date, included for long-running studies with interim reporting of data, supports pharmacovigilance (PV). Other examples include inclusion of selected tabular information in narratives and in-text inclusion of appropriate data rather than cross-referring to appended data. Relatively recent process developments in some larger companies (both sponsors and contract research organisations [CROs]), have resulted in a shift away from purpose-built in-text summary tables, to hyperlinking to end-of-text summary tables only, or direct import of (unedited) statistical outputs to the report body. Whilst no doubt intended to streamline statistical and reporting outputs, such developments may negatively affect the comprehensibility of the intended message, and on a practical level, navigation within the integrated document. As changes in company procedures result in template evolution, the CSRs in an MAA may be structured differently. This could reasonably be expected to impact the work of reviewers both within and between dossiers.

The integrated clinical study report: A multi-component document

Most pharmaceutical companies have their own CSR templates and guidance documents within which ICH E3 is contextualised and interpreted. Although ICH E3 is not a rigid template, the ICH E3 headings are henceforth used for reference purposes. The integrated CSR has two main parts: a 'text part' and an 'appendices' part:

- The text part, written by the medical writer, comprises Sections 1–13 and Section 15. Section 14 contains the end-of-text tables, figures, and graphs – essentially the summary statistical output – as well as clinical narratives, if inclusion in the body of the report would disrupt the CSR flow. The medical writer or drug safety group usually write the narratives.
- The Section 16 appendices comprise study information, data listings, and relevant case report forms. The appendices may be collated and assembled into electronic folders by the medical writer or a document support group. A dedicated publishing group usually electronically integrates the text, Section 14 outputs and narratives, and Section 16 appendices.

The medical writer has a driving role in the preparation of all these components, and must engage with many other functions to produce a high-quality document, delivered on time.

Clinical study report structure and guidance: Text (Sections 1–13 and Section 15) and the statistical outputs (Section 14 and Appendix 16.2)

The definitive guidance for writing CSRs is ICH E3,[2] published in 1995, with supplementary questions and answers (Q&A) published in 2012.[6] For a complete understanding of the current CSR text requirements, the reader is referred to both.

After years of debate about the use of ICH E3 as a definitive template, the Q&A document finally clarifies what experienced CSR authors have long held – that '*ICH E3 is a guideline, not a set of rigid requirements or a template, and flexibility is inherent in its use*'. Restructuring the integrated CSR and appropriate placement of material not specifically covered in the guidelines is welcomed if this improves clarity. At its simplest, this may mean restructuring of text sections in, for example, a phase I safety and pharmacokinetic CSR, and inclusion of the full pharmacokinetic report in an appropriately placed 'ad hoc' appendix. Restructuring for its own sake can lead to differing CSR structures within an MAA which may be unhelpful for the regulatory reviewer.

The CSR text portion comprises a 'front end' section, predominantly methodological, followed by the meat of the document – the 'back end' results (including end-of-text statistical output data), discussion, and conclusion sections. The 'front end' broadly includes a 'stand-alone' synopsis, including key results but devoid of external references (to support its separate publication). Conflicts between ICH E3's maximum suggested synopsis length of three pages and subsequent Common Technical Document M4E guidance[7] of a 10-page maximum are now clarified in the 2012

Q&A document. The basic premise is to apply logic; a synopsis in the region of 10 pages is perfectly acceptable for a more complex study. In addition to the synopsis, the 'front end' should also contain ethical information; trial administrative structure; introduction; objectives; investigational plan (trial methodology); statistical methodology; and changes to the study or planned analyses. Much of the 'front end' material is summarised from precursor documents such as the Investigator's Brochure, protocol, and statistical analysis plan (SAP).

Multiple authors, inevitably with different perspectives and standards, may have contributed to these precursor documents. Note the use of the word 'summarised'. Text should not simply be lifted from the precursor documents, but adapted and repurposed, and written in the past tense, where appropriate. Existing textual information may be better presented in tabular form if this adds clarity and aids comprehension. Cross-referencing certain sections of precursor documents will avoid unnecessary repetition in the MAA. However, care must be taken to cross-reference only accurate original material. If accuracy is in question or text is open to interpretation, better practice is to include abstracted unambiguous information directly in the CSR text.

ICH E6 and ICH E3 were simultaneously developed. However, lack of confluence between requirements in ICH E6 Protocol Section 6.4 'Trial design' and ICH E3 CSR Section 9.2 'Discussion of study design and choice of control groups' can complicate reporting if the rationale behind the study design was not adequately described in the protocol. Such deficits are best addressed by improved protocol template instructional text.[8] CSR Section 9.2 authoring (where Protocol Section 6.4 is deficient) is easier with input from the original protocol development team.

Industry debate about summarising precursor document material in CSRs versus the merits (or otherwise) of only hyperlinking to the original document makes interesting reading (EMWA Group LinkedIn discussion started 08 November 2011, http://www.linkedin.com/groupItem?view=&gid=2717752&type=member&item=79357240&qid=06269034-6116-4370-9846-479f1297d239&trk=groups_items_see_more-0-b-ttl). Current guidance requires population of the relevant CSR 'front end' text sections.

The planned statistical analyses, finalised before locking of the database and described in the SAP, should follow the ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9[9] (henceforth ICH E9). ICH E9 refers the reader to ICH E3. Statistical outputs comprise the summary tables, figures and graphs, and data listings described in the industry as tables, figures, and listings (TFLs). These are most often generated by the statistical team using the 'gold standard' statistical software package, SAS® (http://www.sas.com). TFLs should follow ICH E3's Section 14 and Appendix 16.2 structural guidance to simplify the work of the medical writer and regulatory reviewer. Medical writing review of the SAP before finalisation is highly recommended to ensure confluence of statistical output structure with the guidance documents and to ensure that all summarisations and analyses that the writer might require are planned and programmed in advance.

Writing the 'back end' of the CSR – the results (including end-of-text statistical output data), discussion, and conclusion sections – is driven by availability of final TFLs. It is common to populate in-text summary tables with selected relevant data from the TFLs. The aim is to distil the voluminous output data into easily comprehensible packages of 'results messages', whilst maintaining absolute transparency. This process, if executed analytically and with elegance, should help identify 'signals in the noise'. Presentation of results must be factual; interpretation is not required, except in the discussion. Where sponsors undertake *post hoc* analysis, the appropriate place to report such data are in an *ad hoc* CSR appendix, considering that the only data reportable in a CSR are those for which the analyses were preplanned. If *post hoc* analyses are appended to the CSR, the associated rationale must be included in CSR Section 9.8 'Changes in the conduct of the study or planned analyses'. *Post hoc* analyses can be further reported in a journal article. Supportive analyses (planned, or post-hoc with explanation in CSR Section 9.8) to aid results interpretation, for example, may also be appended. The CSR discussion and overall conclusions section should not restate the results or introduce new results. In short, this section should be a more factually based version of its journal counterpart, with less hypothesising. Superlatives and overstating benefits must be avoided. This section should include discussion of any problems or perceived benefits; place the results into the context of currently available treatment modalities; and refer to ongoing and future development. An understanding of the development plan combined with regulatory insight will assist with preparation of this section. Communication between the CSR author and team members with wider strategic understanding of the product is usually necessary.

Clinical study report structure and guidance: Narratives (Section 14)

Clinical trial data are captured in two separate databases: the PV and clinical databases. The PV database captures safety data that the PV or drug safety group use to produce PV safety narratives on an ongoing basis throughout the study. The clinical database captures all trial-related data including safety data. Once all the data are clean, these two databases should ideally be reconciled. The categories of required CSR narratives are described in ICH E3.[2] CSR narratives are event- and clinical data-based and are distinct from the PV safety narratives which are subject- and PV data-based. PV safety narratives are written using Council for International Organizations of Medical Sciences (CIOMS) forms and are useful in part for preparing the CSR narratives. At reporting, data from the clinical database take precedence over data from the PV database, and this is the reason that data inconsistencies between PV and clinical narratives must be reconciled. Some companies routinely reconcile their PV and clinical study databases, and generate final CIOMS forms from the reconciled database. They place the final CIOMS forms in the CSR *in lieu* of preparing separate CSR narratives. This ensures that the narratives align with clinical data, but remain subject- and not event-based. Identification of the actual event(s) requiring narration may be confounded by this approach. Some categories of narratives may be waived by prior agreement with the regulatory body, for example, deaths, where 'death' is a study endpoint.

When writing large numbers of clinical narratives, analysis programming of subject profiles is a cost- and time-efficient approach worthy of consideration. Subject profiles gather narrative-relevant line listing data for one subject into a single file (similar to US archival listings). Narratives comprehension is aided with selected tabulations (e.g. laboratory data) to break up the prose. Partly tabular narratives also improve project efficiency.

Clinical study report structure and guidance: Appendices (Section 16)

Guidance on the content of CSR appendices is given in ICH E3;[2] instruction on how to adapt the original appendices for CSRs to be included in MAAs was clarified 9 years later in 2004.[10] Further clarification on CSR appendices content appeared in the Q&A document published in 2012.[6] To ensure CSR appendices are fit for inclusion in MAAs, all three guidance documents must be considered.

The resulting requirements now take into account study trial master file (TMF) and clinical supply database content. Although neither is submitted as part of the MAA, the drive to limit CSR appendix content to material necessary for CSR review, results in the 2012 clarification:

> *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.*

The medical writer should remind the responsible team member that the required information must be included in the TMF or clinical supply database by the time of filing of the MAA.

The 'take home' point is that CSR appendices should not be bulked out with redundant documents. In a region where documents used by non English-speaking investigators or subjects must be translated into different languages, local language version documents must not be included in CSR appendices.

The impending public disclosure of full CSRs in 2014 has prompted a shift towards appending details of named individuals formerly included in CSR text Section 6 'Investigators and study administrative structure', as well as the details of the sponsor signatory, to Section 16.

Abbreviated and synopsis clinical study reports

ICH E6 also reminds CSR writers that ICH E3:

> *… specifies that abbreviated study reports may be acceptable in certain cases.*

In the absence of EU-specific guidance, the consensus, supported by Alfaro *et al.* in 2007[11] is to follow the US guidance issued in 1999 by the FDA.[12] Abbreviated CSRs should report selected front-end material; subject disposition information; and crucially, safety data in full. Selected appendices are required with adaptation of the US list by omission of US archival listings.

The 1999 FDA guidance[12] also describes studies for which synopsis reports are acceptable. These are generally studies conducted only in sufficient depth to assess if they cast safety doubt on a product and are often studies for which marketing approval is not being sought. A synopsis report may follow the ICH E3 synopsis format, with supplemental safety discussion (or may substitute synopsis and discussion with published literature), and appended protocol and protocol amendment(s).

Table 1: Guidance documents and resources for content of clinical study reports in the EU: Chronological presentation

Reference number	Document name	Version and date	Web link	Source of and description of document content
Ref. 2	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	http://www.ICH.org 'This document describes the format and content of a study report that will be acceptable in all three ICH regions. It consists of a core report suitable for all submissions and appendices that need to be available but will not be submitted in all cases'
Ref. 1	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1)	Step 4 10 June 1996 (including the post Step 4 corrections)	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf	http://www.ICH.org 'This Good Clinical Practices document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors. and IRBs. GCPs cover aspects of monitoring, reporting, and archiving of clinical trials and incorporating addenda on the Essential Documents and on the Investigator's Brochure which had been agreed earlier through the ICH process'
Ref. 9	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	http://www.ICH.org 'The harmonised tripartite Guideline was finalised under Step 4 in February 1998. This biostatistical Guideline describes essential considerations on the design and analysis of clinical trials, especially the "confirmatory" (hypothesis-testing) trials that are the basis for demonstrating effectiveness'
Ref. 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	Introduction: 'This guidance focuses on the circumstances when full study reports, abbreviated reports, and synopses can be used to submit data concerning the effectiveness of new drugs and biological products'
Ref. 10	CHMP Note for Guidance on the Inclusion of Appendices to Clinical Study reports in Marketing Authorisation Applications	CHMP/EWP/2998/03/Final 23 June 2004	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003638.pdf	Introduction: '…The list of appendices includes a lot of information that may not be necessary for evaluation on a routine basis. Certain of the appendices should be submitted systematically with each report and others should be available on request … the following list has been established as the minimum required'
Ref. 11	Alfaro V, Cullell-Young M, Tanovic A. Abbreviated Clinical Study Reports with Investigational Medicinal Products for Human Use: Current Guidelines and Recommendations. Croat Med J. 2007; 48(6):871–77	December 2007	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2213811/	Abstract: 'Some of the studies conducted during product development may ultimately not contribute to the evaluation of the effectiveness of a product for a specific indication. In these cases, abbreviated Clinical Study Reports are required to be submitted to the regulatory authorities. However, the ICH E3 guideline only provides information on the structure and content of full Clinical Study Reports. A guideline issued by the Food and Drug Administration of the United States in 1999 is the only document available from a regulatory authority that recommends which sections can be included in an abbreviated Clinical Study Report. This article describes which sections have to be included in abbreviated Clinical Study Reports written during clinical development of new medicinal products for human use'
Ref. 6	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	www.ICH.org 'Since reaching Step 4 and publication within the ICH regions, experiences by all parties with the implementation of the E3 Guideline have resulted in the need for some clarification. This supplementary Questions and Answers document intends to clarify key issues. In July 2012, minor typographical errors were corrected in the Answer to Question 6 and the document was renamed R1'

Abbreviations: ICH, International Conference on Harmonisation; IRB, Institutional Review Board; GCP, Good Clinical Practice(s); CDER, Center for Drug Evaluation and Research; CBER, Center for Biologics Evaluation and Research; CHMP, Committee for Medicinal Products for Human Use.

For a complete understanding of abbreviated and synopsis CSR format, the reader is referred to both documents.[11,12]

See Table 1 for current guidelines on full, abbreviated, and synopsis CSR authoring.

Scheduling

A companion guide to CSR authoring is incomplete without considering how to meet the final CSR deadline.

The sponsor will predetermine the date of the final CSR which should take into account the summary results public disclosure requirement of one year after the end of the trial.[1,3] The CSR authors must meet the date by scheduling effectively the preparation of the various components of the integrated CSR. Planning must take into account study complexity and resulting CSR complexity, and an understanding of precursors and drivers (e.g. locking of the database, or availability of final TFLs) for medical writing tasks. CSR complexity is estimated by considering study and reporting variables, such as number of subjects; study phase; indication; number of secondary efficacy variables; number of unique TFLs; and analysis complexity.[13] It takes more time to author a 'high' compared to a 'medium' or 'simple' complexity CSR. Breaking the integrated CSR into smaller deliverables prepared on a timescale to fit with the final CSR deadline is recommended. The 'front end', including unpopulated in-text summary results tables, and appendices should be completed in advance of receipt of the final TFLs, which drive draft reporting. The commonly used strategy of reporting from draft TFLs is not efficient and is not recommended. Draft data changes in the final TFLs will mandate changes in the CSR. Early consideration of the reporting scenario is necessary as reporting postdates clinical, regulatory, and statistical tasks that may be delayed during the project. While it seems reasonable to expect a subsequent delay on the final CSR date, this cannot be assumed, and rarely happens.

There are no industry standard durations for analysis and reporting tasks, as shown by data collected at eight EMWA conferences over 5 years (2008–2013) (see Table 2).

Industry professionals, predominantly regulatory medical writers working for sponsoring pharmaceutical companies, contract research organisations, or independently (freelancers), provided data. Participants were asked to determine typical average durations (in working days, not ranges) in their organisation (or for freelancers, in their experience of working with a range of organisations) for analysis and reporting tasks for a 'moderate complexity',[13] phase III study in 200–400 subjects. Mean (SD) duration for preparation of the first draft CSR from receipt of final TFLs was 16.9 (8.2) working days ($N = 78$) – just over 3 working weeks. The range was 5–45 working days showing how greatly this varies throughout the industry. The draft to final CSR (mean [SD]: 25.7 [21.1]; range: 3–120 working days) timeline was wide ranging, possibly due to the variability in the number of client review cycles between report versions (Table 2).

Table 2: Clinical study report scheduling: Cumulative participant data[a] from eight EMWA conferences 2008 to 2013[b]

Analysis or reporting task for a 'moderate complexity' phase III study in 200 to 400 subjects	N[c]	Duration in working days or number of cycles	
		Mean (SD)	Range
Last subject data in-house to DBL	77	6.6 (5.6) days	1–30 days
DBL to draft TFLs	77	13.9 (9.6) days	1–56 days
Draft TFLs to final TFLs	75	10.6 (6.1) days	1–30 days
Draft CSR authoring from final TFLs to first draft CSR	78	16.9 (8.2) days	5–45 days
First draft CSR to final CSR	78	25.7 (21.1) days	3–120 days
Number of client review cycles	77	2.6 (0.8) cycles	1–5 cycles
QA on final integrated CSR	77	6.6 (5.6) days	1–30 days

Abbreviations: SD, standard deviation; DBL, database lock; TFLs, tables, figures, and listings; CSR, clinical study report; QA, quality assurance.
[a]Data sourced from completed pre-workshop assignments for the advanced EMWA workshop 'Scheduling and proposal writing: the clinical study protocol and report'.
[b]EMWA conferences: Barcelona May 2008; London November 2008; Ljubljana May 2009; Frankfurt November 2009; Lisbon May 2010; Nice November 2010; Paphos May 2012; Manchester May 2013.
[c]Workshop participants providing data.

Algorithm-generated reporting timelines offer a useful guide at the outset of a project; subsequent project-specific refinements add value. When faced with an immovable final CSR date, wider skills of the CSR author must be brought to bear. Persuading colleagues in related but independent functions to adhere to timelines, and managing client expectations, are integral to on-time production of the final CSR.

By understanding the regulatory requirements and utilising project intelligence, medical writers can schedule and author a high-quality, on-time, final CSR for preregistration drug trials in the EU.

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