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An Insider's Insight into Clinical Study Reports

The clinical study report (CSR) is a crucial document in the drug development and regulatory submission process. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E3, a CSR is an integrated report of a study of any therapeutic, prophylactic or diagnostic agent in which the clinical and statistical description, presentations and analyses are provided in a single report, incorporating tables and figures into the main text of the report and in appendices.

To ensure prompt delivery of high quality CSRs, a medical writer needs to both understand regulatory requirements and have the ability to decode the many aspects of the project knowledgebase. We provide here some key learnings from the Niche medical writing team, who have been writing CSRs for the pharmaceutical industry since 1998.

Before you start

The CSR describes the methods and results of a clinical study and provides a short discussion that contextualises the findings.

- Collect the documents identified in the checklist provided in Appendix 1, asking for Microsoft Word versions where possible
- Establish to what extent you plan to follow the guidelines on the report content defined in ICH E3
- Adopt a document template that captures all ICH E3 requirements and maintain a consistent style*
- Guidelines and statutory requirements change. Make sure that you are aware of current requirements before you start

Prepare to succeed

Delay writing the CSR and you risk producing a lower quality report: members of teams move on, the need to reacquaint oneself with the details of a study is inefficient and retrospective reporting can alter perspective and influence data interpretation.

Establish a plan. A CSR often requires contributions, review and approval by various members of the study team. Programme leaders and key operational personnel are usually eager to focus on delivery of the next study just as you need their contribution to the CSR.

Identify all members of the team confirming their roles, responsibilities and commitment to making their contribution to the CSR.

Outline stakeholder-agreed milestones and timelines.

*Our ICH E3-compliant CSR template provides a superb structure in which to report your study findings. Please contact us if you would like a copy.

Reporting requirement

The need to provide a formal report describing the conduct and findings of a clinical study is stated in Section 5.2.2 of the ICH Guideline for Good Clinical Practice E6 (henceforth ICH E6) [1]:

> '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)."

Guidance has also been provided on the structure and content of CSRs [2]:

> '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."

Despite being 20 years old, ICH E3 remains the definitive guidance for writing CSRs [2]; additional direction was provided in the form of a question and answer (Q&A) supplement that was published in 2012 [3]. The guidelines aim to allow the author to write 'a report that is complete, free from ambiguity, well organised and easy to review'.

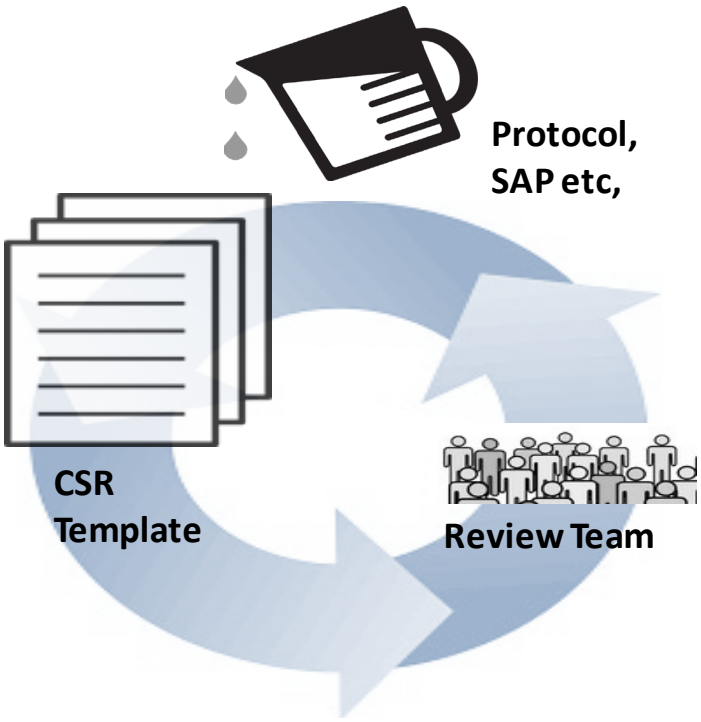
Since 1995 there has been considerable debate over the use of the information provided in ICH E3 as an authoritative template. The 2012 Q&A supplement clarified that ICH E3 should be regarded as a guideline and not a set of rigid requirements or a definitive template [3]. Many organisations regularly involved in conducting clinical trials have their own CSR templates, sometimes with associated guidance documents that describe the interpretation of the ICH guidelines.

The internet is a ready resource for guidance on the structure and content of CSRs; however, equal emphasis is not always given to information provided by different interested parties. An excellent summary of various relevant documents can be obtained from a 2014 report to the European Medical Writers Association (EMWA) [4].

Report construction

Once you have a document template you can prepare a CSR shell. A CSR shell is effectively the 'front half' of the report that incorporates methodological and administrative information from the study conduct documents. Documents that are useful when writing the shell include:

- Relevant report template
- Final protocol and protocol amendments
- File notes (notes explaining specific incidents during the study)
- Study Procedures/Study Reference Manual
- Statistical/Reporting analysis plan
- Details of ethics committee, monitor, laboratories, etc
- Sponsor report writing SOPs/style guides



Once the 'shell' report has been reviewed and approved by the review team it can be locked allowing focus to shift to other sections of the CSR. The results sections can be populated once the data or statistical package becomes available. These are most frequently provided in the form of data tables, listings and figures (TFLs). Although it will depend on the CSR template and study design, study areas that may require their own specific sections within the report include: study population/demographics, safety, pharmacokinetics, pharmacodynamics, efficacy, pharmacogenetics, biomarker data and/or health outcomes.

The purpose of the CSR is to display and discuss relevant findings that have been distilled from the TFLs, drawing attention to possible data signals. The author should also detail any events that were not compliant with the study protocol. Presentation of results must be factual and objective. Figures and tables can be an informative way of illustrating important observations. It is recommended that the body of the report includes in-text summaries of data rather than a list of cross-references to an appended data package.

Any post hoc analyses on the study data should be reported in an appendix to the report as the only data eligible for inclusion in a CSR are those for which the analyses were pre-planned. Supporting analyses to aid the interpretation of results, for example, should also be appended. If post hoc analyses are appended to the CSR, the associated rationale must be included in the section of the report that details changes in the conduct of the study or planned analyses.

The Discussion section of a CSR should avoid simply restating the results. Neither should it be used to introduce data not provided in the results sections. The Discussion should focus on factual review relating to the study objectives and endpoints rather than hypothesising. Use of superlatives and overstating the meaning of your observations must be avoided.

Authors should examine any problems, key learnings or perceived benefits while putting the results into the context of the current development programme. Interaction with the project team should provide a wider strategic understanding of the product and key insights into specific aspects of the report such as statistical and pharmacokinetic interpretation. The Investigator's Brochure may serve as a good source of background information for the Discussion and referencing the scientific literature is permissible. However, heavy referencing of the literature can be indicative of over interpretation and hypothesising.

Scheduling Delivery

Planning achievable timelines and milestones and agreeing them with the project team is essential to ensure timely delivery of your report. The time needed to write the CSR generally depends on the complexity of the study design and the size of the data package. How long it will take to write will also depend on the experience and ability of the writer. It is therefore difficult to predict exactly how long a report 'should' take to write. Keeping in regular contact with the team while you focus on writing the first draft of the CSR keeps the project foremost in everyone's mind.

Splitting a CSR into smaller deliverables, each to be completed on a timescale to fit with the final CSR deadline, is essential. A 'front end' shell, possibly including unpopulated in-text summary results tables and appendices, can be completed in advance of receipt of the statistical data package. However, using partial or draft data sets to prepare the CSR can introduce hard to find errors.

Efficient delivery is benefitted by clear lines of communication. Determine the project team's preferred method of communication; whether that is email, phone or instant messenger. It is worth agreeing with the project team that the 3–10 page 'Study Synopsis' at the front of the CSR will NOT be prepared until the text in the body of the report is considered final. The synopsis will only take a few hours to write and preparing earlier drafts saves little time at the risk of introducing errors.

European Medical Writers Association (EMWA) Study

A survey of medical writers and industry professionals aimed at estimating expected CSR delivery timelines was conducted by EMWA. Participants were asked to determine typical average durations for analysis and reporting tasks for a study of 'moderate complexity' [5]. Basing estimates on a Phase III study conducted in 200–400 subjects a mean (SD) duration for preparation of the first draft CSR from receipt of final TFLs was 16.9 (8.2) working days (N=78). However, the range was broad [5–45 working days] underlining the high variability in delivery times. Estimates for conversion of first draft to final CSR was also wide (mean [SD]: 25.7 [21.1]; range: 3–120 working days). Our own experience suggests that the time it takes to complete a CSR is influenced most by variability in client review times. This also fits with the observations of the EMWA study and underlines the importance of getting early agreement of review milestones and timelines, and ensuring that the team sticks to these.

Insider interview with one of our experienced medical writers

Q Which areas need the most emphasis, detail and explanation?

A I cannot over-emphasise the importance of clarity and attention to detail throughout the report. However, the section on study design often requires some care. It is not normally possible to 'cut and paste' information relating to the design from the study protocol without some modification. Beyond that, you will most likely want to give the greatest emphasis to the primary and secondary endpoints as these represent the pivotal results.

Q What do you think is the most challenging section to write?

A The Discussion can be challenging, particularly in exploratory research studies where the results are highly technical. The reporting and interpretation of the ever-increasing amount of biomarker data can be tricky. Often there is little time available for extensive reading around a topic. In these circumstances it is imperative for a writer to be able to engage with and use the knowledge held within the project team.

Q What qualities should a good CSR writer foster?

A Writers need to be good at managing their time and prioritising their workload, particularly when working on more than one project. If you find yourself running out of time or struggling with a specific aspect of a report it can be beneficial to ask for help. Although some teams are very busy and 'hands off', many are keen to help and welcome this sort of interaction. Do this as early as possible. If something goes wrong, be proactive and identify a way of solving the problem as quickly and efficiently as possible.

Hints and Tips

1. Start promptly

Shell the CSR as soon as possible. Taking time at the start of the project for the team to undertake review of the shell and to agree how key data should be presented will save time later. This also provides an opportunity to identify potential issues and reach a consensus on how best to report on the conduct of the study. However, be careful not to start too early because source documents may change.

2. Where to start

Once you have the data/statistical package it is prudent to start the writing process with the study demographics/population section to familiarise yourself with the study design, subject groups and participation, as well as any important recruitment and/or withdrawal issues that may have arisen during the study. Alternatively, starting with the safety section provides you with a clear understanding of subjects who may have withdrawn from the study for reasons of safety or tolerability. It also gives the author a grasp of the investigational product's safety profile, which you may later relate to pharmacokinetic or pharmacodynamic observations.

3. Project manage

The writing of a CSR is often described under the umbrella term of medical writing. However, when done correctly it is more a specific form of project management.

The writing of a CSR is a process that requires the collection and integration of contributions from multiple sources. Often, these contributions will have been developed by a different 'author' using their own perspectives and standards. The medical writer needs to coordinate delivery of each component, giving themself sufficient time to adapt the contributions to the CSR's requirements, ensuring that the project delivery timelines are maintained.

For the best results the writer must make each member of the delivery team aware of what they are expected to deliver and when it is needed. The experienced medical writer builds a repertoire of friendly emails that can be used to encourage contributors to keep to project timelines and maintain momentum.

4. Discuss and support

The aim of any Discussion is to describe the findings in the context of the current understanding of the study's therapeutic area and the effects of the molecule under investigation. It is not the repository of all knowledge. Reference scientific literature sparingly and use data presented in the CSR to provide support for each of the report's final conclusions. Do not make any grand claims and do not speculate on possible future findings or directions of research. Other submission-related documents are more suited to describing the significance of the results in terms of the overall programme.

5. What to conclude

Conclusions are usually presented as a list of bullet points. They should relate clearly to the objectives and endpoints of the study and should be brief and to the point. You can provide specific conclusions at the end of each of the results sections, repeating all conclusions together at the end of the Discussion section. It should not be necessary to include more than two or three (or four) bullet points per results section.

6. What to do about appendices

Share the list of documents needed for the report with the study project lead at the start of the writing process. Collect documents required for the appendices as early as possible so that retrieval occurs while the body of the report is being written – waiting for documents to be located can delay finalisation of a CSR. Remind the project team that although key study documents may no longer need to be included in the CSR they should be lodged in the Trial Master File. Documents in the appendices can be in PDF or MS Word format. How these documents are incorporated into the final product will depend on the Sponsor's 'publishing' process.

Report appendices

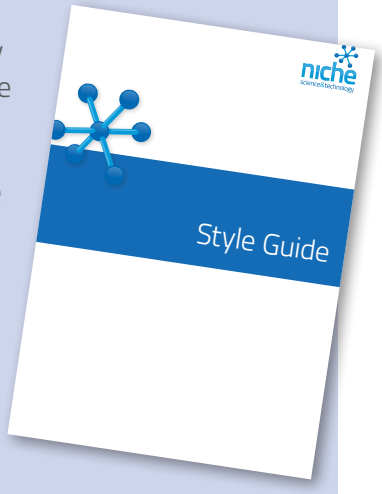
Guidance on the content of CSR appendices is given in ICH E3 [2]; additional information on what is required for CSRs to be included in MAAs was published in 2004 [6], with further clarification given in the 2012 Q&A document [3]. When constructing the appendices for CSRs for regulatory submissions you should give consideration to all three guidance documents. A helpful list is provided in Appendix 2.

Falling under Section 16 of the CSR, appendices comprise study information, data listings and relevant case report forms. Following the 2012 clarification it is now generally accepted that it is not necessary to include supporting documents, such as investigator CVs, ethics committee approvals, informed consent forms, and batch numbers per subject; assuming that these data are in the Trial Master File or clinical supply database. The 'take home' message is that CSR appendices should not be packed with unnecessary documents. For example, if documents used by non English-speaking investigators or subjects have been translated into different languages, local language versions do not need to be included in the appendices.

Note: The introduction of public disclosure of full CSRs within the EU in 2014 prompted a shift of information on named individuals formerly included in CSRs from the body of the report to the appendices.

Using a writing style guide

Writing style guides can be helpful in facilitating the development of CSRs. They ensure that all authors working on a project adopt a similar writing style and provide direction when they may be unclear as to how to proceed. Guides can be a simple sheet of 'do's and don'ts' or complex documents providing instruction on English usage and project specific phraseology. When used across a programme or organisation they serve to standardise the language of clinical source documents and expedite document delivery.



Quality and consistency are at the heart of Niche Science & Technology's philosophy, ensuring a reliable and dependable service. To this end, we have created a series of writing guides in order to ease production, minimise proof corrections and enable schedules to be met. One benefit we have found is a reduction in the time and costs of document preparation.

And finally...

Writing a full CSR represents a major investment of resources and the need to prepare full reports has frequently been debated. The alternate possibility of using shorter abbreviated reports has been proposed and, as ICH E3 states:

> '... abbreviated study reports may be acceptable in certain cases."

However, further guidance is not available for EU submissions leaving Sponsors to decide whether or not they should adopt the proposal of Alfaro et al., who in 2007 [7] suggested that authors follow the US guidance issued in 1999 by the FDA [8]. Abbreviated CSRs should report selected 'front-end' methodology, governance and conduct information; 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 also describes studies for which synoptic reports are acceptable [8]. These are generally studies where the depth of conduct was only sufficient to determine whether or not their findings cast doubt on the safety of a product and are often studies for which marketing approval is not being sought. A synoptic report may follow the ICH E3 synopsis format, with supplemental safety discussion (or may substitute synopsis and discussion with reports published in the scientific literature), appending the study protocol and any amendments.

References

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Appendix 1: CSR essential document checklist

Study protocol and any amendments: a detailed plan for conducting the study. The protocol describes all procedures and endpoints. Amendments record planned changes to the conduct of the study and need to be captured in the description of study conduct.

Study reference/procedures manual: a document that describes in detail the study procedures conducted during the study providing a level of detail not required in the protocol.

Reporting/statistical analysis plan: record of the data to be collected and a plan for how they are to be analysed. It allows the writer to map out text to be included in the body of the report before the data package becomes available.

ICH-compliant CSR template and style guide: Sponsor-dependent documents that can facilitate the development of the CSR depending on the level of guidance and instruction they provide.*

Study data package: tables, figures and listings generated from the data collected during the study and created by the study statistical/data management group.

Miscellaneous supplementary documentation: these might include the study randomisation schedule, file notes, blank case report form, study audit records, lab reference ranges, ethics committee and regulatory authority information, data monitoring committee information (if used).

Note: Studies that involve an investigational medicinal product (IMP) will have an associated Investigator's Brochure. Although it doesn't necessarily include ICH required information it can provide useful information on the investigational medicinal product, such as its characteristics and position in its lifecycle, which may provide useful insight when interpreting the study findings.

Appendix 2: List of CSR appendices

Appendix 16.1.1	Protocol and any protocol amendments
Appendix 16.1.2	Sample CRF (unique pages only)
Appendix 16.1.3	List of IECs/IRBs, information for volunteers, consent forms
Appendix 16.1.4	List and description of investigators and other important staff, including brief (1-page) CVs
Appendix 16.1.5	Signatures of the Principal Investigator and Sponsor's medical officer
Appendix 16.1.6	List of subjects receiving IMP from specific batches, if more than one batch was used
Appendix 16.1.7	Randomisation scheme and codes
Appendix 16.1.8	Audit certificates (if applicable)
Appendix 16.1.9	Documentation of statistical methods
Appendix 16.1.10	Documentation of inter-lab standardisation methods (if applicable)
Appendix 16.1.11	Publications based on the study (if applicable)
Appendix 16.1.12	Important publications referenced in the report (if applicable)

*Our ICH E3-compliant CSR template provides a superb structure in which to report your study findings. Please contact us if you would like a copy.

How can Niche help?

Since 1998, our medical writing team has been working to reduce industry accepted report delivery timelines for high quality CSRs from months to days. For one Blue Chip pharmaceutical company alone, Niche has written over 500 CSRs. Experience highlights the benefits of pharmaceutical companies adopting a medical writing function such as those offered by Niche. Our highly experienced medical writers are eager to support your team, helping you to overcome any acute resource challenges that may otherwise delay your clinical programmes. Anyone can read the guidelines, but can they respond quickly? Niche can.

Next Steps

I hope you found this Insider's Guide useful. We created it to share with you a few pointers and helpful key learnings that we have developed over years of experience. We can also provide you with an ICH-compliant template, which is a great start to writing your own CSR.

Please contact me at the email address below if you would like a copy of our free CSR template or would like further help and advice on writing your CSR. We also run training sessions on how to write CSRs, so please contact me if you would like to know when we will next be running one of these ever-popular training courses.

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