An Insider's Guide to 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, clinical scientists, project managers and/or medical writers need 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 report content guidelines defined in ICH E3
- Adopt a document template that captures the essential 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

Begin writing the CSR as soon as the data are available (if not before): members of teams move on, the need to reacquaint themselves with the details of a study is inefficient and late or retrospective reporting can alter perspective and influence the interpretation of data.

Identify all members of the team, confirming their roles, responsibilities and contributions.
Agree the components to be used and who will be delivering them.

Establish clear milestones and timelines with all stakeholders: CSRs often require 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 at a time when you most need their contribution to the CSR.

*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.

Background

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 over 20 years old, ICH E3 remains the definitive guidance for writing CSRs; 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 its introduction there has been considerable debate over the interpretation of the information provided in ICH E3 as an authoritative template. Taken literally, it serves to create a document that is repetitive and difficult to navigate. The 2012 Q&A supplement clarified that ICH E3 should be regarded more as a guideline than a set of rigid requirements or a definitive template [3]. Consequently, many organisations involved in conducting clinical trials employ their own CSR templates, sometimes with associated guidance documents that describe how the ICH guidelines have been interpreted.

Increasing pressure to disclose the results of studies has also introduced a second purpose for the CSR beyond regulatory reporting, that of public disclosure. Certain 'sensitive' information may be redacted (irreversibly hidden) in CSR employed for public disclosure. This could include key information about the investigational product, methodology and/or subjects under investigation.

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. Beyond the information provided here, an excellent summary of various relevant documents can be obtained from a 2014 report to the European Medical Writers Association (EMWA) and the joint EMWA and American Medical Writers association 2016 CORE reference [4,5].

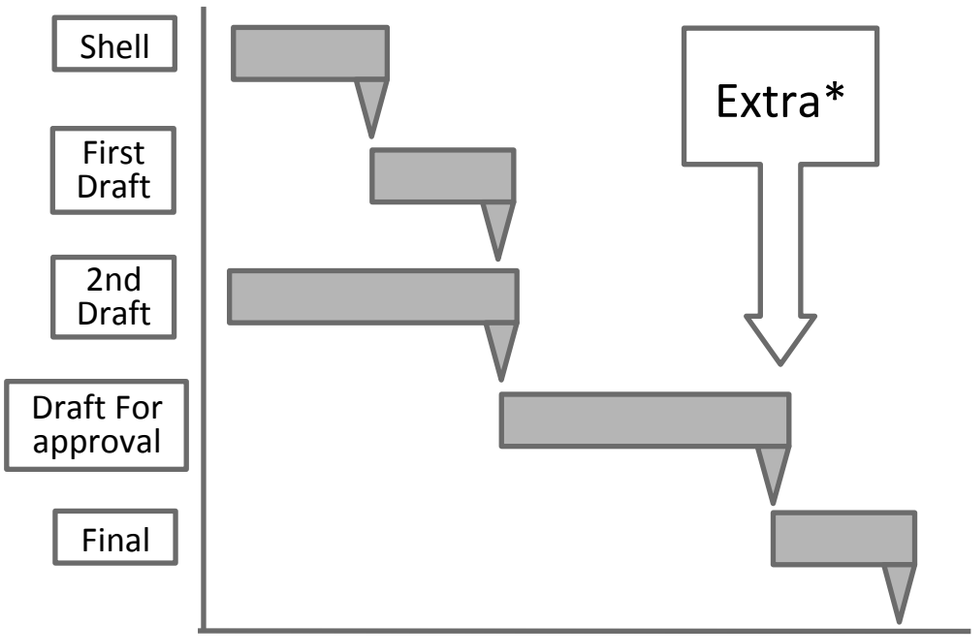
Scheduling delivery

Planning achievable timelines and milestones and agreeing them with the project team is essential to ensure timely delivery of your report. The time it takes to write a CSR generally depends on the complexity of the study design and the size of the data package. It 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 (see European Medical Writers Association Study). 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 a good way to establish milestones. A 'front end' shell, possibly including unpopulated in-text summary results tables (potentially informed by the Reporting Analysis Plan/ Statistical Analysis Plan) and appendices, can be completed in advance of receipt of the statistical data package. However, attempting to save time by using partial or draft data to prepare an early draft of the CSR should be given very careful consideration. There is a high possibility that it will introduce anomalies and errors that will be hard to identify later on in development, requiring a formal and thorough quality check beyond those normally included.

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' [6]. 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.



*Additional review rounds can be added if required. The final version is prepared for sign off by the Principal Investigator and Sponsor's representative

Clear lines of communication ensure efficient delivery. Determine the project team's preferred method of communicating with each other; whether that is email, phone or instant messenger. Finally, 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 in terms of data not matching the final body of the text.

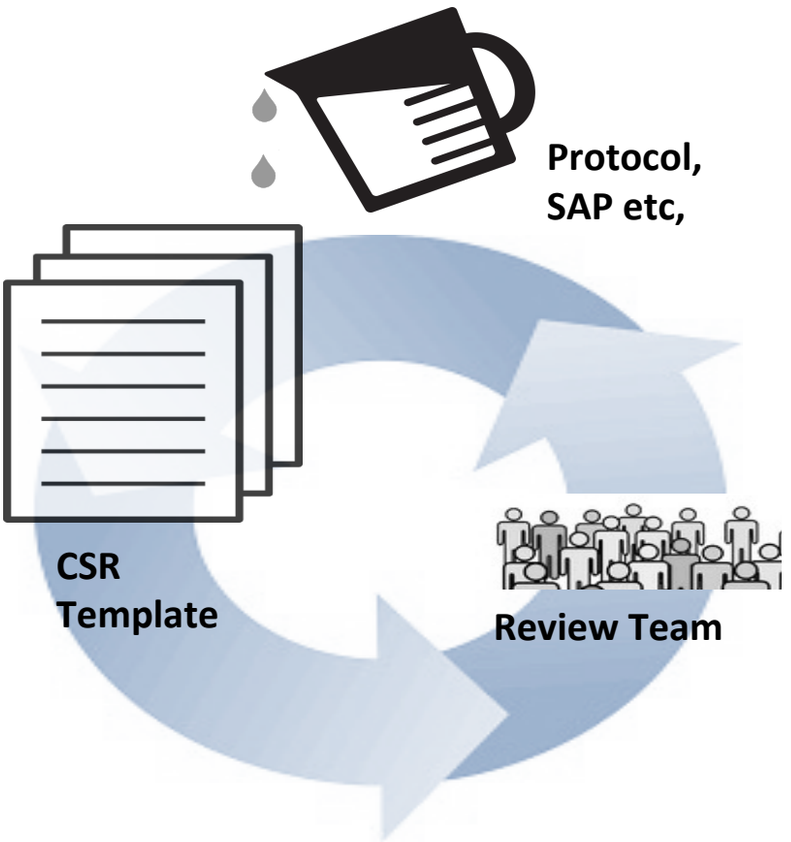
Protocol, amendments, file note and study procedures manual considerations

- The protocol and any amendments are essential. These tell you how the trial was planned
- Ensure the most recent version of the protocol is used, to capture any changes
  File notes are used to clarify or describe situations that arose during the study (small procedural changes)
- The study procedures manual contains useful information on experimental technique that may allow more detail to be added to the report (e.g., dosing instructions, laboratory ranges)

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
- clinTrials.gov registration details
- Details of ethics committee, monitor, laboratories, etc.
- Sponsor report writing SOPs/style guides



Once the team has reviewed and approved the report shell 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, figures and listings (TFLs). Although it will depend on the CSR template and study design, study areas that often require their own specific sections within the report include: study population/ demographics, safety, pharmacokinetics, pharmacodynamics, efficacy, pharmacogenetics, biomarker data and/or health outcomes.

Independently prepared sections provided by pharmacokinetic, pharmacodynamic or statistical specialists (for example) can provide a deeper insight when considering the study findings. Although this can save time for the CSR author, it is essential to allocate a reasonable amount of time to fully integrate these contributions into your master document. Take care to maintain the integrity of the document template structure and style – keep an eye open for broken crosslinks.

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 also 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 the 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.

Navigating report formats

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."

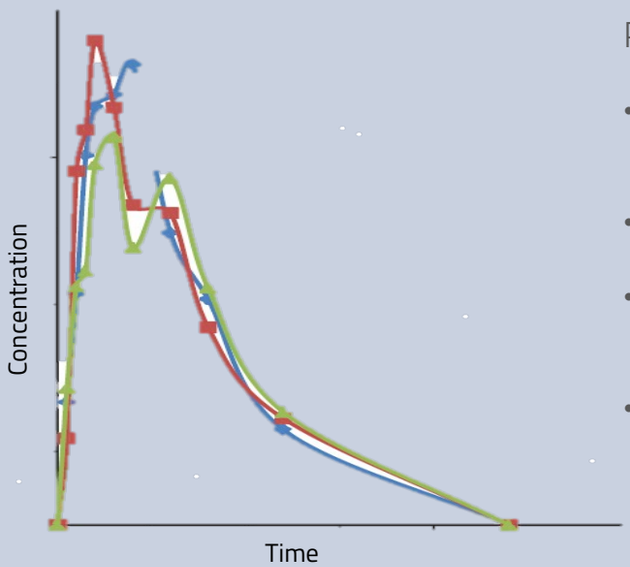
However, further guidance is not available for EU submissions leaving Sponsors to decide whether or not they should adopt the proposal of Alfaro et al., who in 2007 [7] suggested that authors follow the US guidance issued in 1999 by the US Food and Drug Administration (FDA) [8].

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.

Type 1: Full Clinical Study Reports	A comprehensive clinical and statistical description of a sponsor's study conduct. It includes efficacy and safety data. This report format is required if the study is to be used to support approval by a regulatory agency, such as the FDA or European Medicines Agency (EMA), or that support the information in the product label.
Type 2: Supplemental Clinical Study Reports	Provides additional detail to full CSRs, they don't contain all the sections as sponsors see in a full CSR and may, in fact, refer the reader to the main, full CSR. Supplemental CSRs may be created to report planned, but not primary, analyses that were not completed in time to be included in the full CSR, unplanned exploratory analyses, or cross-study analyses.
Type 3: Abbreviated Clinical Study Reports	These condensed versions of the full CSR are generally used for studies not intended to support the efficacy claim for the dose, regimen, population, or indication. These types of CSRs usually contain abbreviated methods and efficacy, but almost always include comprehensive safety.
Type 4: Synoptic Clinical Study Reports*	Synoptic CSRs include summarized disposition/clinical pharmacology/efficacy data from the clinical study and may be acceptable for: • Different indications and dosage forms not being registered • Early safety and tolerability studies, or early bioequivalence studies with early dosage forms • Studies with inadequate design and conduct, uncontrolled studies, or incomplete and discontinued studies • Project and indication close-out reports

*Synoptic reports usually do not contain any in-text tables unless study/reference drugs or information on serious adverse events need a table.



Pharmacokinetic reporting

- Start on least manipulated/analysed data, e.g., plasma concentrations, time profiles
- Move on to derived pharmacokinetic parameters
- Then discuss any further analyses, e.g., dose proportionality, bioequivalence, accumulation
- Cross-refer to safety sections (i.e., are any AEs associated with a spike in drug concentration?)

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 spot potential issues, identify missing documents and reach a consensus on how best to report on the conduct of the study. Be careful, however, not to start too early because some of your source documents may change.

2. Where to start: Determine who got what. 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 writing project management.

   The delivery 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. Use and share our helpful checklist in Appendix 2 to ensure that you have everything covered. The experienced medical writer also builds a repertoire of friendly emails that can be used (repeatedly) to encourage contributors to achieve project timelines and maintain momentum.

4. Protocols – deviations and violations: Detail all deviations - episodes where the activities on a study diverge from the approved protocol. These are usually events that have no significant consequence and do not challenge the overall safety of the subjects. In contrast, protocol violations are divergences from the protocol that materially (a) reduce the quality of completeness of the data, (b) make the ICF inaccurate or (c) impacts a subject's safety, rights or welfare. Examples might include, inadequate informed consent, an unreported serious adverse event or a subject's repeated non-compliance with study requirements. In these cases you can provide short narratives for each subject in CSR detailing violations or tabulate the violations if there are several.

5. 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.

6. 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 section of the results.

7. 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. Start collecting 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 some key study documents may not 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 [9], 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 1.

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.

Sharing data

Data in reports are usually presented in one of three formats: tables, figures or listings.

- Tables: data analysed to varying degrees of complexity, including descriptive statistics and 'testing' (data can often be transplanted directly into the report)
- Figures: graphical representations of the data (usually used sparingly but can be more simple and visually striking than tables)
- Listings: individual values presented by subject are often cited in the text (useful when telling the story of individual subject experiences). Where referring to large amounts of data you may link to the actual listing but this is generally avoided and when you do you might consider raising the source from a Listing to a Table

An interview with an experienced medical writer

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 prefer a 'hands off' approach, many are keen to contribute and welcome this sort of interaction. Establish your teams communication/ support preferences as early as possible. If something goes wrong, be proactive and identify a way of solving the problem as quickly and efficiently as possible.

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 may be highly technical. The reporting and interpretation of the ever-increasing amounts of biomarker data can also be tricky and time consuming. Aggressive timelines often allow little opportunity to undertake extensive reading around a topic. In these circumstances it is imperative for a writer to be able to engage with and use the hive knowledge held within the project team.

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 detailing the 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.

Mandatory reporting

A key principle in the good conduct of clinical trials is that a summary of the trial protocol should be freely available while the study is ongoing and that, on completion of the study. It is now expected that the findings of any study are made readily accessible in a timely fashion. In February 2000, the FDA Modernization Act (1997) prompted the creation of a national clinical trials registry (ClinicalTrials.gov) [10, 11]. Similar databases (such as the ISRCTN) have been established elsewhere. From 2005 the International Committee of Medical Journal Editors (ICMJE) required that clinical trials should be indexed in a clinical trial registry to qualify for publication in a journal following the uniform requirements for manuscripts [12].

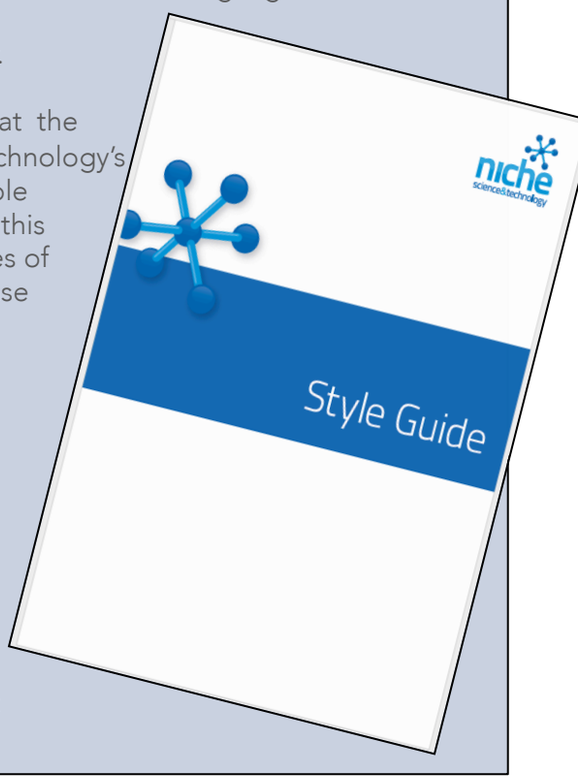
Subsequently, the FDA Amendments Act (FDAAA) of 2007 required registration of summaries of trial protocols for "applicable clinical trials" (trials that are covered by the FDAAA) [13]. These are trials that have at least one site in the United States; are of a drug, device, or biological agent; and are "initiated or ongoing as of September 2007, excluding Phase I studies and early feasibility trials of devices [14].

Clinical trials mustbe registered with ClinicalTrials.gov (clinicaltrials.gov) by 'responsible parties' and uploaded to the website using the Protocol Registration System (http://prsinfo.clinicaltrials.gov). The uploading of trial results is performed in a similar fashion and reviewed by a Protocol Registration System administrator before publication on ClinicalTrials.gov. At present, clinical trials of drugs that already have FDA approval are required to report results within 1 year of completion of the trial (with some provisions for delayed reporting), although in the future applicable clinical trials of unapproved drugs or biological agents that are regulated by the FDA may also be required to report results [15]. These results are posted in the form of a table of values for each of the pre-specified primary and secondary outcome measures for each arm of the clinical trial, with associated statistical tests.

Using a writing style guide

Writing style guides can be helpful in facilitating the development of CSRs. Many well-recognised commercial guides are available (see bottom of page). 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' (often termed writing conventions) 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. We have provided an example of a simple programme writing convention guide, often used by teams writing on a specific molecule of project (Appendix 3).



The EMA also introduced a policy on the publication of clinical data for medicinal products for human use (Policy 0070), in accordance with Article 80 of Regulation (EC) No 726/2004. Policy 0070 was adopted by the EMA Management Board on 2nd October 2014 [16]. Guidance on implementation of the requirements of Policy 0070 were provided by the EMA in 2016 [17]. At the time of finalising this document the EMA had suspended all new activities related to the publication of clinical data due to issues with implementation. It has also stopped sending 'invitation letters' and is contacting companies to cancel new submissions due after 1 August 2018. It is currently noted that the suspension is temporary and EMA will announce when activities are expected to restart [16].

Lay summaries

Ultimately, clinical study reports represent a hitherto mostly hidden and untapped source of detailed and exhaustive data on each trial. Historically, they haven't been available for examination by independent parties interested outside the Sponsor [17]. Openness and accessibility are currently major topics of debate in clinical research. The EMA has mandated preparation of a summary of clinical trials results that are understandable for laypersons [18, 19]. Lay summaries are intended to increase research transparency and to provide the public with the key information about the trial. The 10 elements that must be covered in a lay summary are listed in Annex V of the regulation.

Lay summaries address the general public as well as participating subjects and patients. A summary must be prepared for every clinical trial and be posted on the EU Portal within 12 months after the end of the study. For phase I trials without therapeutic intent, this timeline may be extended up to 30 months. Shorter timelines apply for paediatric trials (6 months).

And finally…

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.

We first developed this Insider's Insight in 2013 to share this know-how with a wider audience. It has remained on the first page of Google search results for information on CSRs since its release, emphasising the value it represents to medical writers, project managers and clinicians alike. We would like to thank all those readers who took the time to provide helpful suggestions on how we might improve on the guidance provided in the previous edition. In the current version we provide additional instruction on content and approach to report delivery as well as a number of helpful checklists.

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 from time to time, 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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Appendix 1: CSR appendices and essential documents

Here are some helpful definitions and lists:

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.

Essential documents list (pre-writing):

- Study protocol and protocol amendments
- Clinical study report template (and any instructions on how to complete it)
- Study reference/procedures manual
- Reporting/statistical/data analysis plan (if applicable)
- Sample CRF/eCRF
- List if IECs/IRBs, information for volunteers and consent forms (including those for protocol amendments)
- Information on any data/safety monitoring committee, including the name and address of the chairperson

Study data package: tables, figures and listings (often termed TFL's) generated from the data collected during the study and created by the study statistical/data management group.

- Clinical data as tables, figures and listings
- Safety (adverse event and serious adverse event) narratives (if applicable)
- Milestone study dates/timing – e.g., date of first subject-first visit etc.

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

Note: The protocol may refer to key references from the scientific literature that will be useful when preparing the CSR. Remember to include them in the list of references if you cite them in the report. It may be necessary to include copies of these publications in the appendices if they play a significant role in interpretation of the report data. Studies that involve an investigational medicinal product will have an associated Investigator's Brochure.

Although it doesn't necessarily include ICH required materials it can provide useful information on the investigational medicinal product, such as its characteristics and position in its lifecycle, which may provide helpful insight when interpreting the study findings.

Appendix 1: CSR appendices and essential documents (continued)

Publishing the final CSR is often not left to the medical writer in large commercial organisations. However, in smaller companies the writers may be expected to coordinate collection of all aspects of the full CSR and manage its compilation into a single document (file). Below is a useful guide to the structure and content of report 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)

If you find yourself responsible for coordinating the compilation you will be best advised to start collecting (or attempting to collect) the various supporting documents at the earliest available date. Key data that often overlooked until the last minute include:

- Certificates of analysis
- Documentation on laboratory ranges and inter laboratory standardisation methods
- Data on different IMP batches used and who got what if subjects were switched between groups
- Investigator CVs (single-page)
- Any scientific publications based on the study

And don't forget to collect and include the Sponsor and Investigator signature pages.

Appendix 2: CSR Finalisation Quality Checklist

Issue:	✓
Document header same throughout	
Title – same in all places (Title page and signature pages)	
Remove all track changes (accept/reject)	
All Protocol amendments included (and ICFs etc.)	
Spell check – American/English (as appropriate)	
AEs (episodes or events clearly defined)	
Bullets:	
Correct format	
Start with capital, end with full stop	
List:Num: restart numbering with each section	
Cross links and reference to sources:	
Tables	
Figures	
References	
Tables:	
Caption heading, left justified, capital letters, no abbreviations	
Gridlines (uniform throughout)	
Table width (uniform throughout)	
Ranges in [square] brackets	
Abbreviations defined	
Source data noted	
Time and events table included	
Abbreviations:	
None in headings	
Abbreviations and numbers written in full at the beginning of sentences	
Defined at first use (synopsis and report)	
Plurals (AEs not AE's)	
Layout and format (printout or reduce page size):	
No repeated heading titles (e.g., primary objectives, primary endpoints)	
Hard space/hyphen – breaks over page/line	
Section headers not split over a page	
Correct font throughout	
Single spaces at the beginning of sentence	
En dash [ranges]	
Time periods hyphenated (e.g., 3-h reading)	
Read for sense	
"Compared with" vs. "compared to" used appropriately	
Past tense throughout	
Punctuation correct	
Updated Table of Contents	
Finalise	

Appendix 3: Writing convention – example

SUBMISSION WRITING CONVENTIONS FOR Niche's Sparkling Lemonade

General
Always refer to product as 'The Lemonade'.

All clinical documents (e.g., clinical study reports [CSRs], clinical trial register summaries [CTRS], clinical CTD summaries, and Investigators Brochures [IB]) must be created in Microsoft Word using the correct Niche Science & Technology Ltd. template.

The Niche Science & Technology Ltd. of Style should be used as a resource for questions regarding writing style that are not addressed in this document.

The term 'subject' is to be used rather than 'patient'.

Style:
- The term 'adverse event' is used rather than 'adverse experience'.
- Capitalize all treatment groups;
- Upper case first letters will be used when referring to specific study days/visits, e.g., 'Day 1', 'Day 3–5' or 'Visit 1'; an en dash will be used between numbers of days, e.g., 3–5. When quoting extended visit windows hyphens may be replaced to avoid confusion e.g., Day -2 to Day 1.;
- Gender– caps (e.g., Male, Female);
- Race – capitalize (e.g., White, Black, Hispanic);
- Use UK spelling for reports used in the UK and US English spelling for reports prepared in the US. Words using US spelling within the template boiler plate text do not need to be changed to UK spelling for reports written within the UK and vice versa

Numbers
The European convention for dates is used (e.g., 01 January 2019 or 31-Jan-2019).
For whole numbers from one to nine, words rather than numerals are used, except when used in conjunction with units (e.g., 10 mg/L) or percentages (e.g., 10%) or when referring to a specific time point (e.g., 3 hours, Day 2).

For numbers greater than or equal to 10, numerals are used, except at the beginning of a sentence (e.g., Fifty subjects participated...).

A comma is not used for numbers greater than 1000 and less than 10,000 (e.g., 1500 not 1,500). A comma is used for numbers greater than 10,000.

Probability values are expressed as lower case 'p' without a space (e.g., $p=0.001$ or $p<0.005$).

Abbreviations
The following are examples of abbreviations that are suitable for use in the text and tables without being defined:
- Units - kg, mg, µg, mL and so on for all SI units, U for arbitrary units, IU for international units;
- Other standard abbreviations - IV, SC, PO, OD, MD, PRN, AM, PM, ITT, PP, bid, i.e., e.g., Mr, Dr, etc.

SUBMISSION WRITING CONVENTIONS FOR Niche's Sparkling Lemonade (cont.)

In addition, the following are suitable for use in in-text tables (but not the text without explanation)
- Year(s), month(s), week(s), day(s), hour(s), minute(s) and second(s) should be abbreviated to y, mo, w, d, h, min, sec, respectively
- Use M for male and F for female
- N=sample size; n=subset of sample size
- Standard deviation and confidence interval can be abbreviated to SD and CI, respectively

Other standard abbreviations to be used include:
- Adverse event: AE
- Serious adverse event: SAE

Appendix 3: Writing convention – example (continued)

Spacing

Do not use spaces when citing percentages e.g., 43%.

When citing ranges use a dash without spaces on either side (e.g., 55–65 ng), do not use the word 'to'.

Hyphens, em and en dash

Use a hyphen (dash without spaces on either side) in compound words that are used attributively to clarify the unification of the sense. For example:

- child-bearing; drug-related adverse event; Fifty-one subjects; on-therapy; placebo-controlled, double-blind, parallel-group study; Gram-negative; intent-to-treat; pre-dose, pre-therapy, post-dose, post-therapy.
- Hyphens should not be used for: per protocol; post menopausal; HIV positive
- The en dash (longer than the hyphen) is used to denote span in page ranges, unit values, and dates. It is also used as a link between two nouns.
- The em dash (longer than the en dash) is used in place of parentheses or to introduce an afterthought or a statement to summarize what has gone before.

Bullet Points/Numbered Lists

End a series of bullets with semi-colons, with the exception of the last bullet, which should be ended with a period. Example follows:

- one;
- two;
- three;
- four.