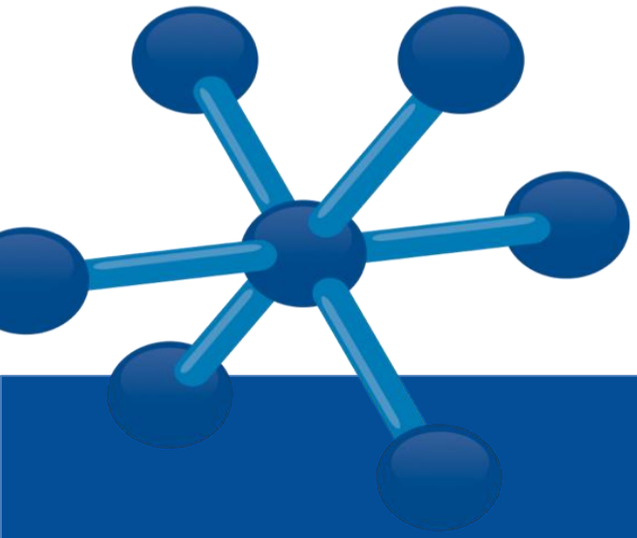


An Insider's Insight into Clinical Study Reports

The clinical study report (CSR) is a crucial document in the drug development and regulatory submission process. According to the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E3, a CSR is an integrated report of a trial 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 decode the many aspects of the project knowledge base. We provide here some key insights 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 trial 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 trial 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 trial team. Programme leaders and key operational personnel are usually eager to focus on delivery of the next trial protocol at a time when you most need their feedback on the CSR.

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

Background

The need to provide a formal report describing the conduct and findings of a clinical trial is stated in Section 3.17.2 of the ICH Guideline for Good Clinical Practice E6(R3) (henceforth ICH E6) [1]: "Whether the trial is completed or prematurely terminated, or an interim analysis is undertaken for regulatory submission, the sponsor should ensure that the clinical trial reports, including interim 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 ICH E3." Despite being almost 30 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 about interpreting ICH E3 as an authoritative template. Applied too literally, it can result in documents that are repetitive and difficult to navigate. The 2012 Q&A clarified that ICH E3 should be viewed as guidance rather than a rigid set of requirements or a fixed template [3,4]. As a result, many organisations conducting clinical trials use their own CSR templates, often supported by internal guidance describing their interpretation of ICH principles.

Growing pressure to disclose clinical trial results has introduced a second role for the CSR beyond regulatory submission: public disclosure. In this context, certain sensitive information may be redacted, including details relating to the investigational product, methodology, or participants. However, redaction should not compromise data utility, and information of high value should be preserved wherever possible.

The internet provides extensive guidance on CSR structure and content, though sources vary in authority and emphasis. In addition to the materials discussed here, comprehensive overviews are available in a 2014 report to the European Medical Writers Association (EMWA) [5] and the joint EMWA–American Medical Writers Association CORE Reference Manual published in 2016 [6].

Following the United Kingdom's departure from the European Union in 2020, EU regulations were retained in UK law, and the EU Clinical Trials Regulation entered into application in 2022, applying to all new and ongoing trials. As CSRs are the primary regulatory documents summarising trial findings, regulatory changes directly affect their content and disclosure requirements. The UK Medicines and Healthcare products Regulatory Agency (MHRA) became a full ICH member in 2022, and further updates to UK Clinical Trials Regulations are expected in Spring 2026. These evolving frameworks may introduce additional expectations for CSR transparency and disclosure, requiring medical writers to remain alert to regulatory change.

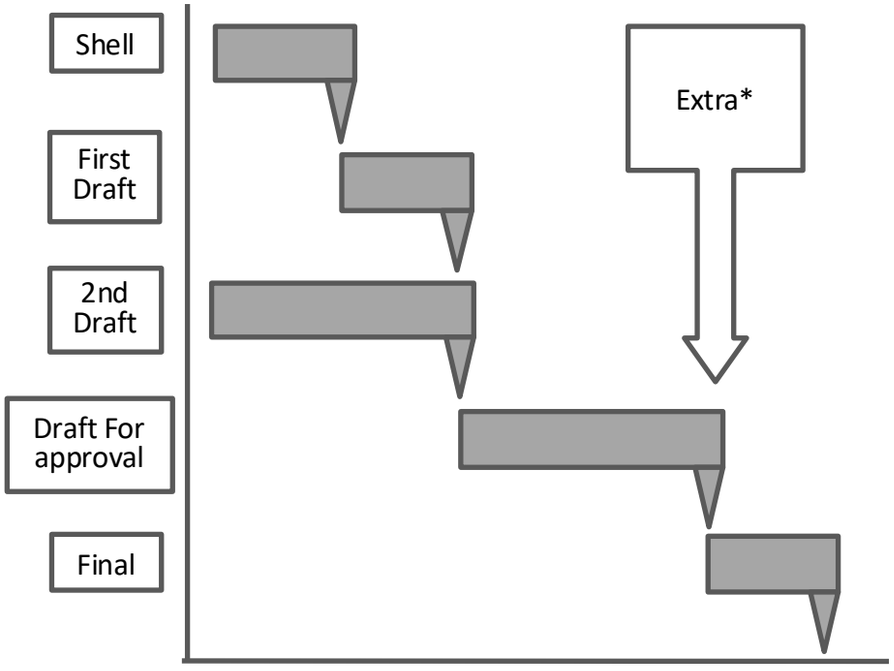
Scheduling Delivery

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 trial 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 EMWA Study box to the right). 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 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 trial of 'moderate complexity' [7]. Basing estimates on a Phase III trial conducted in 200–400 participants a mean (SD) duration for preparation of the first draft CSR from receipt of final tables, figures and listings (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 signoff by the Principal Investigator and Sponsor's representative

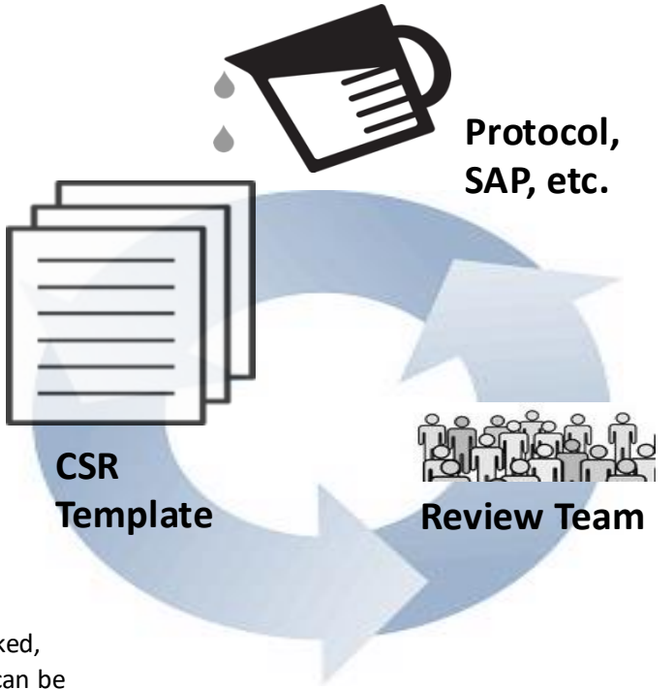
Set up a responsibility-assignment framework to clearly define who does what in the writing process, actions or decision making, clarifying scientific ownership, interpretive authority, and escalation pathways for unresolved issues.

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 to 10 page 'Synopsis' at the front of the CSR will NOT be prepared until the text in the body of the report is considered near 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 trial 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 trial (small procedural changes)
- The trial 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 trial 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 trial)
- Trial Procedures Manual
- Statistical Analysis Plan
- ClinicalTrials.gov registration details
- Details of ethics committee, trial monitor, laboratories, etc.
- Sponsor report writing standard operating procedures/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 tables, figures, and listings (TFLs).

Although it will depend on the CSR template and trial design, trial areas that often require their own specific sections within the report include: trial 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 trial 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.

A CSR's purpose is to display and discuss findings distilled from the TFLs, drawing attention to possible data signals. Authors should detail any events that were not compliant with the trial protocol. Presentation of results must be factual and objective. Figures and tables are 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 or end-of-text data package. Any post hoc analyses on the trial data should be reported in a separate section as the CSR should focus on the analyses that were pre-planned. If post hoc analyses are included in the CSR, the associated rationale must also be included in the section of the report that details changes in the conduct of the trial 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 trial objectives and endpoints rather than hypothesising. Use of superlatives and overstating the meaning of your observations must be avoided. Writers should adopt a hypothesis driven narrative structure, clearly linking objectives, endpoints, analyses, and conclusions. Claims should be explicitly supported by referenced evidence tables and figures.

Authors should examine any problems, key findings 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.

Risk-based Authoring Considerations

All interpretive statements in the CSR should be traceable to source TLFs, which in turn should map to SAP defined analyses. Claim-to-evidence mapping tables are recommended for inspection readiness. The CSR should be authored with explicit awareness of its integration with the Clinical Overview, ISS/ISE, Investigator's Brochure updates, and labelling narratives to ensure claim consistency across the submission. Not all CSR sections carry equal regulatory weight. Primary efficacy analyses, key safety summaries, protocol deviations, and missing data handling should be prioritised for senior scientific review and enhanced quality control (QC) process. CSR authors should also consider downstream requirements for public disclosure, redaction, and lay summaries during document development to minimise rework and compliance risk.

Navigating Report Formats

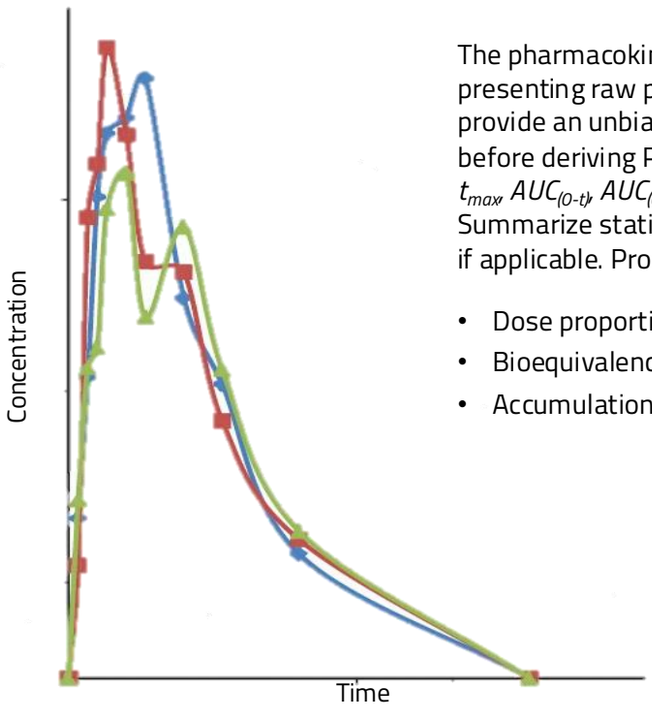
Writing a full CSR represents a major investment of resources and the need to prepare full reports has frequently been debated. The alternate possibility of using shorter abbreviated reports has been proposed and, as ICH E3 states: "… abbreviated study reports may be acceptable in certain cases." However, 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 [8] suggested that authors follow the US guidance issued in 1999 by the US Food and Drug Administration (FDA) [9].

Abbreviated CSRs should report selected 'front-end' methodology, governance and conduct information; participant 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 trials for which synoptic reports are acceptable [9]. These are generally trials that were only sufficient to determine whether or not their findings cast doubt on the safety of a product and are often trials 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 trial protocol and any amendments.

Type 1: Full Clinical Study Report	A comprehensive clinical and statistical description of a sponsor's trial conduct. It includes efficacy and safety data. This report format is required if the trial 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 Report	Providing additional detail to full CSRs, this report type does not contain all the sections sponsors see in a full CSR and may, in fact, refer the reader to the main, full CSR. A supplemental CSR 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-trial analyses.
Type 3: Abbreviated Clinical Study Report	This condensed version of the full CSR is generally used for trials not intended to support the efficacy claim for the dose, regimen, population, or indication. This type of CSR usually contains abbreviated methods and efficacy, but almost always includes comprehensive safety.
Type 4: Synoptic Clinical Study Report*	A synoptic CSR includes summarised disposition/clinical pharmacology/efficacy data from the clinical trial and may be acceptable for: • Different indications and dosage forms not being registered • Early safety and tolerability trials or bioequivalence trials with early dosage forms • Trials with inadequate design and conduct, uncontrolled trials, or incomplete and discontinued trials • Project and indication close-out reports

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



Best Practices for writing up the pharmacokinetic analyses

The pharmacokinetic section of a CSR should begin with the least manipulated data, presenting raw plasma concentrations and time profiles (e.g., linear/log-linear plots) to provide an unbiased overview of drug exposure [10]. This establishes a foundation before deriving PK parameters. Next, report key pharmacokinetic parameters (e.g., C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $t_{½}$), calculated using non-compartmental analysis or modelling [11]. Summarize statistics (geometric means, CV%) and compare across doses/demographics if applicable. Proceed to secondary analyses, such as:

- Dose proportionality (power model or ANOVA on dose-normalised AUC/C_{max}) [12].
- Bioequivalence (90% CI for AUC/C_{max} ratios, if applicable) [13].
- Accumulation (e.g., ratio of Day 7/Day 1 AUC).

Finally, cross-reference safety data to assess whether AEs correlate with pharmacokinetic metrics (e.g., C_{max}-related toxicity, trough-dependent side effects) [14]. Highlight any concentration-QTc or exposure-response relationships if analysed. This structured approach, from raw data to derived parameters and integrated safety, ensures clarity and regulatory compliance [2].

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 review 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 trial. Do not forget to include estimands, where available, alongside the objectives. 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 trial demographics/population section to familiarise yourself with the trial design and participant groups, as well as any important recruitment and/or withdrawal issues that may have arisen during the trial.

   Alternatively, starting with the safety section provides you with a clear understanding of participants who may have withdrawn from the trial 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 also a specific form of writing project management. The delivery of a CSR is a process that requires the collection and integration of information from multiple sources. Often, the protocol and SAP will have been developed by a different 'author' using their own perspectives and standards. The delivery date for the TFLs can be delayed due to unforeseen issues. 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 and updated as required.

   For the best results, a 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 some of our helpful pointers in Appendix 2 to aid in your reviews; this is just a selection of the many checks that we do in-house. 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. During writing it is important to monitor re-write rates, query density for key sections, number of review cycles and any inspection findings linked to the writing.

4. Protocols, minor and major deviations: Deviations are episodes where the activities on a trial diverge from the approved protocol. These are usually events that have no significant consequence and do not challenge the overall safety of the participants, i.e., minor deviations. In contrast, major (or important) deviations are divergences from the protocol that materially (a) reduce the quality of completeness of the data, (b) make the Informed Consent Form inaccurate or (c) impact a participant's safety, rights or welfare. Examples might include inadequate informed consent, an unreported serious adverse event or a participant's repeated non-compliance with protocol requirements. In these cases, you can provide short narratives for each participant in the CSR detailing deviations or tabulate the deviations 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 trial's therapeutic area and the effects of the molecule under investigation. It is not the repository of all knowledge. To make the CSR disclosure-ready, avoid using participant IDs as per Policy 0070 recommendations. 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 results significance in terms of the 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 trial 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 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 trial 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.

Quality Control

Quality control processes are integral to achieving this outcome and must extend beyond technical accuracy checks. Inspection-ready QC should explicitly support the integrity of the regulatory narrative by documenting not only what was reviewed, but why key interpretive decisions were made. Review records (like the tracked document revisions and data we record on Tracker at Niche) should capture the rationale for substantive revisions, the resolution of scientific disagreements, and the justification for inclusion or exclusion of analyses. Version histories must be complete and traceable, enabling inspectors to reconstruct the evolution of the document and to understand how final conclusions were reached.

In this context, QC functions as a safeguard for scientific credibility and regulatory trust. It provides assurance that the CSR is not only accurate and compliant, but also thoughtfully constructed, internally coherent, and aligned with the totality of evidence submitted to regulators. By maintaining clear documentation of review decisions and interpretive judgement, sponsors and authors demonstrate control over the narrative, accountability for conclusions, and readiness to defend the submission during regulatory review or inspection.

AI-Assisted Authoring

Artificial intelligence (AI) language generation models (LLMs) are revolutionizing writing tasks. It is crucial therefore to consider the ethical concerns that come with their use and how they are deployed [15]. AI tools and LLMs may be employed to assist with limited, clearly defined tasks during CSR development. These include the generation of preliminary draft text derived strictly from structured inputs such as approved protocols, statistical analysis plans, and final tables, listings, and figures; consistency checks across sections of the CSR; and support for language clarity, formatting, and adherence to established templates. In all cases, AI-generated content is considered draft material only. It must be critically reviewed, verified against source data, and substantively edited as necessary by a qualified medical writer prior to inclusion in any regulatory submission.

The use of AI tools for scientific interpretation or regulatory judgement is explicitly prohibited. AI systems must not independently interpret efficacy or safety data, assess causality, perform benefit–risk evaluations, or generate conclusions or discussion text without direct human authorship. AI tools may not replace named authors or signatories, nor may accountability for CSR content be delegated to an automated system. These restrictions are consistent with ICH E3 guidance, which places responsibility for the accuracy and integrity of clinical study reports on the sponsor and designated experts, and with regulatory positions that accountability for regulated documentation cannot be transferred to AI technologies [15].

Decisions regarding whether AI assistance is appropriate for a given CSR task should follow a documented, risk-based framework. Factors to be considered include the scientific and regulatory significance of the task, the potential impact of errors, the transparency and reproducibility of AI outputs, and the ability of a qualified human reviewer to independently verify content against source documents. Only tasks that are descriptive, non-interpretive, and fully reviewable are considered suitable for AI assistance, consistent with emerging regulatory expectations for trustworthy AI use in medicine development [16,17].

AI tool use must be transparent, controlled, and auditable. Records should document the AI system used, its intended purpose, the nature of the input data, and the scope of its contribution to the CSR. Evidence of human review, validation checks, and final approval must be retained.

Human accountability

A named, appropriately qualified author retains full responsibility for the scientific accuracy, completeness, and regulatory compliance of the CSR. Final approval must be provided by responsible clinical and statistical signatories, who confirm that the report faithfully represents the underlying data and clinical context. The use of AI does not modify or diminish these responsibilities. In accordance with the joint principles articulated by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), AI is regarded as an enabling technology that augments human expertise but does not replace it, and accountability remains with the human actors involved [16].

Validation activities should address known AI risks, including hallucinations, embedded bias arising from training data, and variability in outputs when identical prompts are reused. These controls align with regulatory principles for data integrity, reproducibility, and bias risk management, as reflected in EMA, FDA, and international guidance on AI and computerised systems used in regulated environments [16,17,18].

Prompt governance forms part of the overall control framework. Prompts should be designed to constrain outputs to factual, source-derived content and should be managed in a controlled manner where feasible. Where required by sponsor policy or regulatory expectation, the use of AI tools in CSR development should be disclosed transparently during inspections or in response to regulatory queries, consistent with principles of transparency and good documentation practice [16,18].

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 trial is ongoing. On completion of the trial, it is expected that the findings 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) [19, 20]. Similar databases (such as the ISRCTN and the EMA's Clinical Trials Information System [CTIS]) 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 [21].

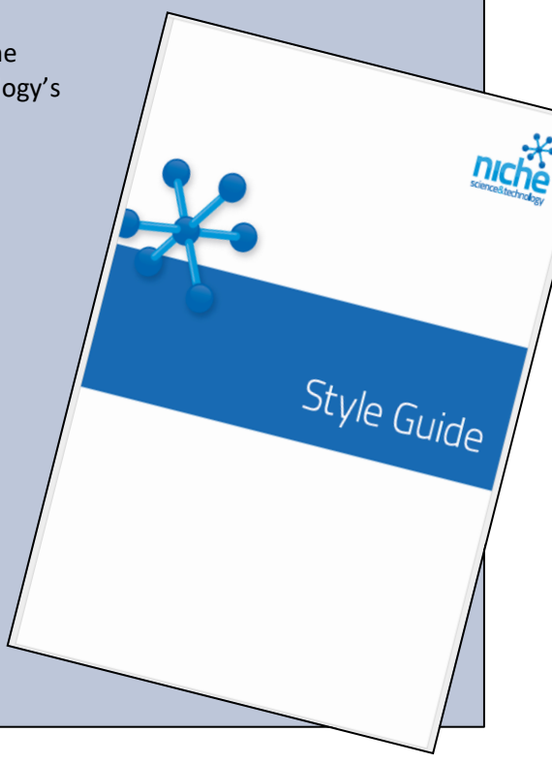
Subsequently, the FDA Amendments Act (FDAAA) of 2007 required registration of summaries of trial protocols for "applicable clinical trials" (trials that are covered by the FDAAA) [22]. These are trials that have at least one site in the United States; are of a drug, device, or biological agent; and are "initiated or ongoing as of September 2007, excluding Phase I studies and early feasibility trials of devices [23].

Clinical trials must be registered with 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. Since 2007, clinical trials of drugs that have FDA approval have been required to report results within 1 year of completion of the trial (with some provisions for delayed reporting) [24]. Under the FDA's Final Rule of 2017, applicable clinical trials of unapproved drugs or biological agents that are regulated by the FDA are now also required to report results. 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 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 or project (see 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 first adopted by the EMA Management Board in 2014 [25], implemented in 2016 [26] and updated in 2019 [27]. The policy was paused after the UK left the EU and during the COVID-19 pandemic. Policy 0070 was relaunched in 2024 for medicines with new active substances that were the subject of an initial MAA from September 2023 onwards. The EMA plans to expand activities from April 2025 to encompass all new MAAs including negative opinions, withdrawn applications, line extensions (i.e., new formulations of existing products) and major clinical Type II variations (i.e., new indications for existing products) [28].

Patient-Reported Outcomes

Patient-reported outcomes (PROs) have become increasingly critical in clinical trials, providing direct insights into patients' experiences with symptoms, treatment side effects, daily functioning, and health-related quality of life (HRQoL) [29]. Historically, clinical trials focused primarily on clinician-assessed endpoints, but regulatory agencies, including the FDA and EMA, now emphasize PROs as key secondary or even co-primary endpoints, particularly in chronic and symptomatic diseases [30]. A well-designed clinical trial protocol must define PROs clearly, specifying the rationale for their inclusion, the instruments used, and the statistical analysis plan [31]. PRO measures must be validated to ensure reliability, responsiveness, and relevance to the target population [32]. Frequently used tools, such as the EQ-5D for HRQoL or the FACIT-Fatigue scale for symptom burden, undergo rigorous psychometric testing before implementation [33].

In the clinical study report (CSR), PRO results should be contextualized alongside traditional efficacy and safety data. Even if primary clinical endpoints (e.g., progression-free survival) remain unchanged, improvements in PROs, such as reduced symptom severity or enhanced treatment satisfaction, can significantly influence patient adherence, perceived benefit, and long-term outcomes [34]. For example, in oncology, a therapy that maintains stable disease but improves pain control may substantially enhance patient well-being despite no change in tumour response [35].

Thus, integrating PROs into trial design and CSR interpretation ensures a patient-centric approach, aligning regulatory and clinical decision-making with real-world patient needs [36].

Maintaining Integrity

Regulators do not read CSRs as data repositories but as decision documents supporting conclusions on benefit–risk, evidentiary strength, and clinical relevance. Maintaining data integrity therefore requires clear traceability from every scientific statement to verified sources and a transparent, auditable pathway from data to conclusion.

Effective CSR production depends on structured workflows that document stakeholder interactions throughout the document lifecycle. These workflows should capture the origin of analyses, the rationale for interpretive statements, and the resolution of scientific or methodological issues, demonstrating that conclusions result from controlled, multidisciplinary review rather than undocumented judgement.

Source-to-statement traceability is central to this process. Factual assertions and interpretive claims must be linked to approved source materials, including the protocol, statistical analysis plan, and final tables, listings, and figures. Documented review and sign-off enable regulators to reconstruct the evidentiary chain with confidence.

Data integrity also underpins decision quality by reinforcing hypothesis-driven interpretation. CSR narratives should align with prespecified objectives, clearly distinguishing confirmatory from exploratory findings. Documenting why analyses are emphasised or contextualised ensures that the benefit–risk narrative remains logically constructed and proportionate to the evidence.

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 [26]. 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 [37, 38]. 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. The UK Health Research Authority also requires a lay summary to be prepared [38]. Please contact us if you are interested in learning more about our lay summary template.

Lay summaries address the general public as well as trial participants. A summary must be prepared for every clinical trial and be posted on the EU Portal within 12 months after the end of the trial. For phase I trials without therapeutic intent, this timeline may be extended up to 30 months. Shorter timelines apply for paediatric trials (6 months). Detailed instructions on how to prepare lay summaries can be found in our Insider's Insight [39].

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 Marketing Authorisation Applications (MAAs) was published in 2004 [40], 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 trial 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 participant; 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 participants 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 participant are often cited in the text (useful when telling the story of individual participant 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 team's communication/ support preferences as early as possible. Track and record all activities. 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. Build the trial story arc (problem→hypothesis →evidence →conclusion).

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 trial design often requires some care. It is not normally possible to 'cut and paste' information relating to the design from the trial 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 within the claims hierarchy.

And Finally…

The preparation of a Clinical Study Report is not merely an exercise in documentation, nor a mechanical assembly of tables, listings, and figures. At its core, CSR development is an act of scientific synthesis: the careful construction of a coherent narrative that explains what was done, what was observed, and what the findings mean in the context of regulatory decision-making. A well-written CSR transforms complex clinical data into regulatory insight by presenting a structured, transparent, and logically reasoned account of the trial that supports assessment of benefit–risk, evidentiary robustness, and interpretability [1,2].

Effective CSR writing relies on a clear scientific 'story arc.' This arc begins with the rationale for the study and its objectives, progresses through the design choices and conduct of the trial, and culminates in the presentation and interpretation of results. Each stage must be connected explicitly, so that outcomes are demonstrably linked back to prespecified objectives and hypotheses, and deviations or limitations are acknowledged and contextualised. This approach reflects principles long recognised in regulatory science: that evidence is most persuasive when it is logically chained, internally consistent, and transparently reasoned rather than merely exhaustive.

Central to this process is evidence chaining, the deliberate alignment of data sources to support defined claims. Individual analyses, subgroup findings, and safety observations should not be presented as isolated facts, but as components of a structured hierarchy of evidence that cumulatively supports regulatory conclusions. Claims regarding efficacy, safety, or tolerability must be proportionate to the strength of the underlying data, clearly distinguishing confirmatory findings from supportive or exploratory observations. This hierarchy allows regulators to assess not only what the data show, but how confidently conclusions may be drawn, and under what assumptions or limitations.

Scientific storytelling in the CSR does not imply persuasion at the expense of objectivity. Rather, it reflects disciplined narrative construction grounded in methodological rigour and transparency. The discussion section, in particular, plays a critical role in integrating results across endpoints, populations, and analyses, explaining concordance or divergence, and situating findings within the broader development programme. When executed effectively, this narrative supports downstream regulatory documents, including the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE), by ensuring conceptual alignment, consistency of claims, and continuity of interpretation across the submission.

Ultimately, the Clinical Study Report should be understood as both a comprehensive record of trial conduct and a structured scientific argument. When underpinned by rigorous methodology, coherent storytelling, and robust quality processes, the CSR becomes a powerful tool for regulatory decision-making, enabling reviewers to assess benefit–risk with confidence and to understand the evidence in a way that is transparent, logical, and reproducible.

Next steps

I hope you found this Insider's Insight useful. We created it to share with you a few pointers and helpful key insights 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:

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

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

SAP: 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):

- Trial protocol and protocol amendments
- Clinical study report template (and any instructions on how to complete it)
- Trial reference/procedures manual
- Statistical/data analysis plan (if applicable)
- Sample CRF/eCRF
- List of 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

Data package: tables, figures and listings (often termed TFLs) generated from the data collected during the trial and created by the trial statistical/data management group.

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

Miscellaneous supplementary documentation: these might include the participant screening log, trial randomisation schedule, file notes, blank sample case report form, trial 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.

Trials 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 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 trial (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 are 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 which participants received them
- Investigator CVs (single-page)
- Any scientific publications based on the trial

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

Appendix 2: CSR Finalisation Quality Checklist

Issue	✓
Page headers same throughout	
Title – same in all places (Title page, and signature pages and synopsis)	
All protocol amendments included	
Spell check – American/British English (as appropriate)	
Bullets	
Correct format	
Start with upper case letter, do not end with full stop	
Numbered lists: restart numbering with each section	
Cross links and references to sources	
Tables	
Figures	
References	
Tables	
Caption heading, left justified, sentence case, no abbreviations	
Borders (uniform throughout)	
Table width (uniform throughout)	
Abbreviations defined	
Source data noted	
Schedule of assessments/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 (set zoom to whole page)	
No repeated heading titles (e.g., primary objectives, primary endpoints)	
Hard space/hyphen – breaks over page/line	
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	

Appendix 3: Writing conventions – example

SUBMISSION WRITING CONVENTIONS FOR NICHE'S SPARKLING LEMONADE

General
Always refer to the product as 'the Lemonade'.

All clinical documents (e.g., protocols, clinical study reports [CSRs], Common Technical Document [CTD] summaries, and Investigator's Brochures [IB]) must be created in Microsoft Word using the correct Niche Science & Technology Ltd. template.

Our extensively tested and refined in-house Medical Writing Style Guide should can be used as a resource for questions regarding writing style that are not addressed in this document. Please contact us if you are interested in learning more about our full style guide.

Some pointers from our style guide are included below.

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

Style:
- Capitalise all treatment groups
- Upper case first letters will be used when referring to specific days/visits, e.g., 'Day 1', or 'Visit 1'; an en dash will be used between numbers of days, e.g., Days 3–5. When quoting extended visit windows hyphens may be replaced to avoid confusion e.g., Day -2 to Day 1
- Race and ethnicity – capitalise (e.g., White, Black or African American, Hispanic)
- Use UK spelling for reports used in the UK and US English spelling for reports prepared in the US. However, when a report follows US spelling, retain the Medical Dictionary for Regulatory Activities (i.e., UK) spelling in the medical history and adverse events in-text tables

Numbers
The European convention for dates is used (e.g., 01 January 2025 or 01-JAN-2025).
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 participants were enrolled…).

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 or equal to 10,000.

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

Abbreviations
A word or phrase to be abbreviated should appear in full at the first mention, followed by the abbreviation in parentheses: magnetic resonance imaging (MRI). Generally, words or phrases should only be abbreviated if they are used at least three times in the document. Abbreviations used in the synopsis should appear again in full at the first mention in the main body of the text. Do not use an abbreviation at the start of a sentence; instead, spell it out even if it has previously been defined.

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).

Appendix 3: Writing conventions – example (continued)

SUBMISSION WRITING CONVENTIONS FOR NICHE'S SPARKLING LEMONADE (Continued)

Hyphens, em and en dashes

Hyphens are used to aid clarity, especially in compound adjectives:

- Pre- and post-dose; dose-dependent effect; long-term trial; double-blind trial
- Hyphens should not be used for: well known fact; chemically induced effect; highly motivated individual (never hyphenate after a word ending in -ly)
- 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 of equal weight
- The em dash (longer than the en dash) is used in place of parentheses or to introduce an afterthought or a statement to summarise what has gone before

Bullet Points/Numbered Lists

Start each bullet point with an upper-case letter; do not use punctuation at the end of the bullet points:

- One
- Two
- Three
- Four