CORE Reference (Clarity and Openness in Reporting: E3-based)

– a tool for modern clinical study reports in an era of increasing transparency and disclosure

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Abstract

CORE Reference (www.core-reference.org) facilitates the authoring of a content-driven clinical study report (CSR) that is as "public disclosure-ready" as possible. It has potential to increase the quality of final CSRs and enhance consistency within and between sponsors.

The ever-burgeoning regulatory guidance document substructure contains content requirements mandated subsequent to the International Council for Harmonisation (ICH) E3 guidance that must be worked into CSRs; these are integrated into CORE Reference. It is also the only known freely-available resource that pinpoints the sections in an ICH E3-compliant CSR that are potentially affected by public disclosure considerations.

Two years on from its initial release in May 2016, the developers of CORE Reference review the growing utility of this important tool, and place it into the context of the current global era of increasing data transparency and disclosure, where policies and guidelines in development beyond European borders will further mandate carefully authored CSRs for sharing in a global public arena.

Introduction

Any guidance or reference material reflects requirements at a static time point. The clinical study report (CSR) has its origins in the 1995 International Council for Harmonisation (ICH) regulatory guidance document ICH E3 on the structure and content of CSRs,[1] and the 2012 ICH E3 supplementary Questions & Answers (Q & A).[2] However, modern clinical study designs often integrate pharmacokinetic, pharmacodynamic, pharmacoeconomic and pharmacogenomic elements with a safety and efficacy backbone. To meet today's complex clinical-regulatory requirements, clinical studies need a fit-for-purpose reporting framework that may differ substantially from that of the more straightforward efficacy and safety studies of 20 years ago, which ICH E3 set out to support. In addition, the ever-burgeoning regulatory guidance document substructure contains additional content requirements that must be worked into CSRs. Even the most experienced and laterally thinking CSR author must be extraordinarily diligent and well informed to keep pace. Specifically, the new area of public disclosure of CSRs, now mandated in the European Union, is worthy of mention. This has profound effects on the way that CSRs must now be written. European Medicines Agency (EMA) guidance on preparing clinical data for public disclosure[3] explains that masking confidential or sensitive information using black-box redaction methods alone will "decrease clinical utility of the data compared to other techniques", so it strongly encourages the move towards other anonymisation techniques. The impacts on the CSR are multiple and complex, and lessons will be learned as CSRs are disclosed in increasing numbers.

The global push for data transparency increases potential utility of CORE Reference

Regulators around the world are following EMA's lead on public disclosure of clinical data. Health Canada's draft guidance[4] on public release of clinical information – to support proposed changes[5] to the Food and Drug and Medical Device Regulations – is open for public consultation until June 25, 2018; the US FDA announced plans to publish CSRs in a pilot scheme "…to evaluate whether disclosing certain information included within CSRs following approval of a NDA improves public access to drug approval information." The plans indicate that the CSR body, protocol and statistical analysis plan will be shared. When the pilot is concluded, CSR portions will be publicly posted.[6]

The (European) General Data Protection Regulation (GDPR)[7] – enforced on May 25, 2018[8] – has far-reaching implications for the safe sharing of clinical trial data. Article 2 states:

> The principles of, and rules on the protection of natural persons with regard to the processing of their personal data should, whatever their nationality or residence, respect their fundamental rights and freedoms, in particular their right to the protection of personal data…

Overlaps between regulatory public disclosure requirements and compliance with GDPR will become clearer in the fullness of time.

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As a result of all of the above, CSR authors face increasing challenges of creating CSRs that support heterogeneous study designs, whilst covering all of the important and emergent content requirements, including current and future public disclosure requirements.

CORE Reference presents focused CSR structure and content addressing current regulatory guidances, including public disclosure

ICH E3 and the 2012 Q & A do not mandate a template order of presentation for design elements, but allow flexibility in structuring the CSR appropriate to individual study design. In the absence of a common approach, a CSR framework for individual studies inevitably results in wide variability in report structures.

CORE Reference (www.core-reference.org) was developed as an open-access "user manual" to help CSR authors navigate the relevant guidelines so they can create CSRs that are relevant for today's studies.[9] The ICH E3 Q & A 2012[2] document states unequivocally that ICH E3[1] is a guidance document and not a template. Similarly, CORE Reference is a user manual and not a template. Multiple, extensive and rigorous literature searches were conducted throughout the project to support the broad aim of integrating relevant global and regional (EU and USA) regulatory guidance into the CORE Reference document. Thus CORE Reference presents a suggested focused structure and content that addresses the current guidance documents and also provides insights and suggestions for anonymisation techniques and approaches that will minimise redaction requirements in the publicly disclosed CSR. CORE Reference is the only known freely-available resource that pinpoints the sections in an ICH E3-compliant CSR that are potentially affected by public disclosure considerations.

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To allow easy mapping to the original ICH E3 guidance document and to avoid conflict with guidance documents that refer to ICH E3 sectional numbering, CORE Reference maintains the level 1 heading hierarchy of ICH E3. It remains at the author's discretion to decide on the most appropriate CSR structure beyond that, although CORE Reference provides some helpful guidance based on the experience of its development team.

CORE Reference credentials

The CORE Reference manual was created over a two-year period by a group of highly experienced experts in ICH E3, CSR templates, CSR authoring, and the public disclosure of clinical-regulatory documents. These individuals included employees of pharmaceutical companies and contract research organisations, as well as freelancers, who were brought together in an attempt to represent the range of perspectives of professionals commonly engaged in authoring clinical-regulatory documents. A statistician and clinical pharmacologist also joined the team at a later date to ensure that all areas had expert input. The CORE Reference initiative was supported by the European Medical Writers Association (EMWA) and the American Medical Writers Association (AMWA). It was registered with EQUATOR[10] (Enhancing the QUAlity and Transparency Of health Research) Network, which is an international initiative that seeks to improve the reliability and value of published health research literature by promoting transparent and accurate reporting and wider use of robust reporting guidelines. Stakeholders were also involved in the review of the draft CORE Reference document, and included experts from a global industry association, regulatory agency, patient advocate, academic and Principal Investigator representatives.

Understanding CORE Reference utility

CORE Reference comprises a Preface, followed

by the actual resource. The Preface clarifies intended use and underlying principles that inform resource utility. The Preface lists references contributing to development of the resource, which broadly fall into "regulatory" and "public disclosure" categories. The CORE Reference document includes ICH E3 guidance text, ICH E3 Q & A 2012-derived guidance text and CORE Reference text, distinguished from one another through the use of shading.

All ICH E3 guidance text is either included as original wording; or is included as modified wording and the modification is explained; or is omitted, with the omission being shown and the reason for the omission explained. All ICH E3 Q & A 2012-derived guidance text is included and explained. Rationale comments – in "comment balloon" format on the right-hand side of each page – are used for explanation and clarification purposes. A key explaining text shading and comments is included in the footer of each page of CORE Reference. Where alternative presentations of the same information would work equally well in a CSR, they are shown with an explanation provided in the Rationale comments to allow CSR authors to make informed authoring choices relevant for their particular study. A separate mapping tool comparing ICH E3 sectional structure and CORE Reference sectional structure is also provided. Together, CORE Reference and the mapping tool constitute the user manual. CORE Reference is provided as a PDF. The separate mapping tool is provided in spreadsheet format to support its utility.

It is important to note that CORE Reference was developed using a proactive approach to the complex area of CSR disclosure since it was observed that the pharmaceutical industry was developing a two-step process for submitting and then publishing clinical study results. This two-step process involves producing a submission-ready CSR that may contain sensitive data that must be removed after submission to produce the final disclosure-ready CSR. The "primary use CSR" (the EMA term is scientific review version)[3] is a technical document for regulatory review and comprises full CSR text and all CSR appendices. The "secondary use CSR" (the EMA term is redacted clinical report)[3] is for public disclosure and comprises redacted CSR text and selected appendices. Sensitive information presented in the primary use CSR is redacted in the secondary use CSR. CORE Reference proposes that the CSR should be as disclosure-ready as possible from the outset to safeguard against inadvertent identification of participants or commercially confidential information, assure optimally timed public disclosure of clinical trial results, and be as cost efficient as possible. The latest available guidance on public disclosure of clinical-regulatory documents has been integrated into CORE Reference through discrete colour-coded comments prompting the user to consider both the primary and secondary use CSR. These guidance comments incorporated into CORE Reference should help CSR authors make informed choices as they navigate the evolving and complex area of redaction of sensitive information prior to public disclosure.

With sufficient uptake, it has potential to drive standardisation of the writing of CSRs across the industry.

Growing awareness

CORE Reference has been actively taken up within pharmaceutical companies and contract research organisations (CROs), with over 12,000 downloads of CORE Reference and over 5,600 downloads of the mapping tool between May 2016 and May 2018). Several organisations have adapted it into a template for use with their standard operating procedures (SOPs). With sufficient uptake, it has potential to drive standardisation of the writing of CSRs across the industry.

Of course, any resource can only remain relevant if it is updated on an as-needed basis. This is a stated aim for CORE Reference.[9] Some 4 months after CORE Reference was launched, the US Department of Health and Human Services published the Final Rule on clinical trials registration and results information sharing,[11] effective January 18, 2017, which mandates the registration and submission of summary results from clinical trial results information in clinicaltrials.gov (www.clinicaltrials.gov) for certain clinical trials of drugs (including biologic products) and devices. Although the detailed requirements will not impact results reporting in CSRs *per se*, signposting to these requirements (as already done for similar EudraCT results posting requirements) in a future version of CORE Reference is expected to add tangible value for sponsors in managing registry postings alongside the writing of CSR results content. Ongoing due diligence of the evolving regulatory landscape will also support future updates of CORE Reference.

In summary, CORE Reference facilitates the authoring of a content-driven CSR that is as disclosure-ready as possible. It should also increase the quality of final CSRs and enhance consistency within and between sponsors. It may also benefit systematic reviewers in their use of CSRs and provide a useful resource for auditors on all the current guidance documents associated with a CSR. The CORE Reference website (www.core-reference.org) also supports sharing of feedback, as well as providing regular news updates after sign up at http://www.core-reference.org/subscribe. The website is a living resource that archives CORE Reference-related print publications and audio-visual media following live presentations. A "Coming Soon" section supports educational planning needs.

Conflicts of interest

Both authors are freelance medical writers and have no conflicts of interest to declare.

References

1. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports E3. Step 4. 1995. http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.

CORE Reference is a user manual and not a template.

Accessed 24 Oct 2017.

2. ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers (R1) 6 July 2012. http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html. Accessed 24 Oct 2017.
3. External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use. Revision 3 – Adopted Guidance. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_ content_ 001799.jsp&mid=WC0b01ac 0580b2f6ba. Accessed 15 Feb 2018.
4. Health Canada. Public release of clinical information - Draft guidance document. https://www.canada.ca/en/health-canada/programs/consultation-public-release-clinical-information-drug-submissions-medical-device-applications/draft-guidance.html Accessed 31 May 2018.
5. Health Canada. Public release of clinical information. 13 April 2018. https://www.canada.ca/en/health-canada/programs/consultation-public-release-clinical-information-drug-submissions-medical-device-applications.html Accessed 31 May 2018.
6. FDA Clinical Data Summary Pilot Program. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm589210.htm Accessed 31 May 2018.
7. General Data Protection Regulation (GDPR) Portal. https://www.eugdpr.org/. Accessed 15 Feb 2018.
8. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&qid= 1490179745294&from=en. Accessed 15 Feb 2018.
9. Hamilton S, Bernstein AB, Blakey G, Fagan V, Farrow T, Jordan D, Seiler W, Shannon A, Gertel A, Budapest Working Group: Developing the Clarity and Openness in Reporting: E3-based (CORE) Reference user manual for creation of clinical study reports in the era of clinical trials transparency. Research Integrity and Peer Review. 2016. http://dx.doi.org/10.1186/s41073–016–0009–4. Accessed 19 February 2018.
10. EQUATOR Network. CORE Reference Tool (Clarity and Openness in Reporting: E3-based) http://www.equator-network.org/reporting-guidelines/core-reference/. Accessed 24 October 2017.
11. US Department of Health and Human Services. Final Rule. Clinical trials registration and results information sharing. https://s3.amazonaws.com/public-inspection.federalregister.gov/2016–22129.pdf. Accessed 24 Oct 2017.

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With over 30 years in pharmaceutical and CRO environments, **Debbie Jordan** set up a medical writing group in a large CRO, growing her 7-strong team over 4 years, before establishing her own freelance medical writing and clinical research service enterprise. Debbie was a key member of the CORE Reference development team.