Streamlining Clinical Study Protocols and Reports

Recent pharma initiatives have been established to help ensure that clinical study protocols and reports are always presented in a similar way, making for easier assimilation and assessment. This article discusses these initiatives, and outlines their key recommendations.

By Sam Hamilton at Sam Hamilton Medical Writing Services and Julia Forjanic Klapproth at Trilogy Writing & Consulting

As we have seen in earlier articles in this magazine, ICH guidelines help ensure that the same critical types of information are included in appropriate clinical documentation (including clinical study protocols [CSPs] and clinical study reports [CSRs]), but they do not guarantee that this information is always presented in a similar way. This means that regulatory reviewers have to interpret numerous documents about all kinds of medicines, which may differ not only because of their specific therapeutic area content requirements, but also because information requirements that are common across programmes are presented in different ways. It is therefore difficult to gain a clear understanding of the data generated across an industry. The effort needed to extract and compare data from one programme to the next – even within a single therapeutic area – can be enormous. Despite this, the reviewer must assess if each new drug would be a valuable addition to the existing armamentarium of medicines.

In the past 12 months, two initiatives have come to fruition that will help streamline the writing of CSPs and CSRs. These are the TransCelerate Common Protocol Template (CPT) and the CORE (Clarity and Openness in Reporting: E3-based) Reference. Both aim to produce CSPs and CSRs of common structure and layout, with standard information in just one, consistent place. They aim to simplify the review task enormously and improve transparency, making it immediately apparent if information is missing or incomplete. The goal is to save time in developing documents and in drug development generally, as writing teams dispense with discussing options for the structure of the standard elements of a particular document, and focus on content. So is this a pipe dream?

TransCelerate Common Protocol Template

The new CPT was issued by TransCelerate in December 2015 (1). The TransCelerate group is a collaboration between industry stakeholders and regulators who had the idea of producing a definitive template for the CSP, regardless of the type of treatment or therapeutic area being studied. Each company approaches CSP writing slightly differently: should the description of all the variables be in the statistics section

What is the TransCelerate CPT?

The CPT is a detailed protocol template, including pre-prepared headings and draft text, in Microsoft Word format. It is intended to be used directly by authors of CSPs for any kind of clinical study, involving any kind of medical condition or therapy. The goal is that all protocols present equivalent information in a similar manner. The Word template contains sections marked as common text or text that may be employed across CSPs with little to no editing if the author so chooses. Clearly, the use of the template is at the discretion of the author.

For the preparation of a CSP, the CPT implementation toolkit includes the resources listed in the table below (2):

Resource	Description	Comments/value of using
Word CPT Guidance for use	A detailed Word document that contains instructions and brief videos demonstrating selected steps in the use of the technology-enabled edition of the CPT	Provides understanding of the functionality found in the technology-enabled edition of the CPT
Frequently asked questions	Frequently asked questions and responses about the CPT, how it was developed and how it will be maintained	Access to responses on common questions
Mapping exercise – instructions and worksheet	A tool to facilitate comparison of an existing protocol template to the CPT	Allows for section-by-section identification of differences in headings and content to aid in assessing impact of implementation and possible mitigations needed
Stakeholder map	A customisable tool to assess the impact that implementation of the CPT may have on each stakeholder group	Allows those implementing to plan for appropriate training and communication needs
Text colour guide	Colour coding used within the CPT to distinguish common, suggested example and instructional text	Provides understanding of the meaning of colour coding used

or in the investigational plan section? Where should details of the various parties involved in performing the clinical study appear – in an appendix, at the front or somewhere in the middle? As long as the information is there, its location is immaterial – as evidenced by the fact that CSPs are approved and the studies run, despite all this variation. So why not agree on one approach, and use the time saved to focus on other, more important things? Training medical writers would be less time-consuming; writing and review time would also be shortened.

So what does the TransCelerate CSP template give us? At a minimum, it offers a model CSP template defining a common structure and standardised language. Its intended use with libraries of common language in areas specific to patient populations and therapeutic areas means that the pre-crafted text proposals for many sections will be the same across CSPs. Ultimately, the industry can save the time spent pondering redundancies and instead focus on study-specific content. Co-author and end user review will be streamlined as familiarity with these standardised texts grows. Regulatory reviewers will more rapidly navigate to the meaningful, study-specific content and comparison of CSPs across programmes will be enhanced, such that the input from ethics committees/ institutional review boards and regulators will be more focused. Investigators and study staff will more readily find the information they need, which may translate to efficiencies in terms of study performance.

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CORE Reference

Another new tool – released in May 2016 for CSRs – is CORE Reference, designed to streamline the way the industry structures and populates a CSR. The international basis for CSR content is laid out in the 1995 ICH regulatory guidance document ICH E3 on the structure and content of CSRs (3), and the 2012 ICH E3 supplementary Q&As (4). However, any guidance or reference material is reflective of a static time point and, back in 1995, clinical studies were simpler than they are today. Modern clinical study designs often integrate pharmacokinetic, pharmacodynamic, pharmacoeconomic and pharmacogenomic elements with a safety and efficacy backbone. Today’s clinical studies need a fit-for-purpose reporting framework that may differ substantially from the more straightforward efficacy and safety studies of 20 years ago, which ICH E3 set out to support.

The ever-growing regulatory guidances dictate additional content requirements that must be worked into CSRs. The medical writer must be extraordinarily diligent and well informed to keep pace. Specifically, public disclosure of CSRs – now mandated in the EU – has profound effects on the way that we must write CSRs. EMA guidance on preparing clinical data for disclosure explains that because redaction alone will “decrease clinical utility of the data compared to other techniques”, it strongly encourages the move towards proactive anonymisation techniques (6). The impacts on the CSR are multiple and complex, and lessons will be learnt as CSRs are disclosed.

What is CORE Reference?

CORE Reference is a user manual to help medical writers navigate guidelines as they create CSR content relevant for today’s studies. It comprises a preface followed by the actual resource, which includes the following:

- Text from the original ICH E3 guidance document is shown in unboxed grey shading
- Text from the ICH E3 Q&A 2012 guidance document is shown italicised, grey shaded and boxed
- CORE Reference text is not shaded and not boxed

A separate mapping tool compares ICH E3 sectional structure and CORE Reference sectional structure. Together, CORE Reference and the mapping tool constitute the user manual (5).

Key Areas in which CORE Reference adds to ICH Guidelines

CORE Reference makes content suggestions for the primary use CSR (the EMA term is ‘scientific review version’). Comments are used to indicate individual report text portions that may potentially impact the secondary use CSR (the EMA term is ‘redacted clinical report’) and should, therefore, be considered for redaction in the secondary use CSR – for public disclosure.

CORE Reference mapping tool provides the sectional structure of CORE Reference, but the important areas where CORE Reference advises restructuring and greater granularity of CSRs are as shown in the table which follows:

ICH E3 section	Key CORE Reference section differences
8 – Study Objectives	New granularity: 8.1 – Objectives 8.2 – Endpoints
9.4.1 – Treatments Administered	New granularity: 9.4.1.1 – Investigational Products 9.4.1.2 – Non-Investigational Products
9.5.1 – Efficacy and Safety Measurements Assessed and Flow Chart	New granularity: 9.5.1 – Efficacy and Safety Measurements Assessed and Schedule of Assessments 9.5.1.4 – Safety – Adverse Events 9.5.1.5 – Safety – Clinical Laboratory Evaluation 9.5.1.6 – Safety – Vital Sign Measurements 9.5.1.7 – Safety – Physical Examination 9.5.3 – Pharmacokinetic and Pharmacodynamic Measurements 9.5.3.2 – Pharmacokinetic Parameters 9.5.3.3 – Pharmacodynamic Measurements 9.5.3.4 – Pharmacodynamic Parameters 9.5.4 – Other Measurements
9.7.1 – Statistical and Analytical Plans	New granularity: 9.7.1 – Statistical Plans 9.7.1.1 – General Approaches 9.7.1.2 – Primary Efficacy Endpoint Methodology 9.7.1.3 – Secondary Efficacy Endpoint Methodology 9.7.1.4 – Other Efficacy Endpoint Methodology 9.7.1.5 – Safety Endpoint Methodology 9.7.1.6 – Pharmacokinetic and Pharmacodynamic Endpoints Methodology 9.7.1.7 – Other Endpoint Methodology
9.8 – Changes in the Conduct of the Study or Planned Analyses	New granularity: 9.8.1 – Changes in the Conduct of the Study 9.8.2 – Changes in the Planned Analyses 9.8.3 – Changes Following Study Unblinding and Post-hoc Analyses
11.1 – Data Sets Analysed (Efficacy Section)	Moved to 10.3 – Data Sets Analysed – new Study Subjects, Section 10
11.2 – Demographic and Other Baseline Characteristics (Efficacy Section)	Moved to 10.4 – Demographic and Other Baseline Characteristics – new Study Subjects, Section 10. New granularity added: 10.4.1 – Demography 10.4.2 – Baseline Disease Characteristics 10.4.3 – Medical History and Concurrent Illnesses 10.4.4 – Prior and Concomitant Treatments
11.3 – Measurements of Treatment Compliance (Efficacy)	Moved to 10.5 – Measurements of Treatment Compliance in Study Subjects – new Study Subjects, Section 10
11.4 – Efficacy Results and Tabulations of Individual Patient Data	Becomes Section 11.1 – Efficacy Results
11.4.1 – Analysis of Efficacy	Becomes Section 11.1 with new granularity: 11.1.1 – Primary Efficacy Endpoint 11.1.2 – Secondary Efficacy Endpoints 11.1.3 – Other Efficacy Endpoints 11.1.4 – Post-hoc Analyses
11.4.6 – By-Patient Displays	Not included
12 – Safety Evaluation	ICH E3 Section 12.1 – Extent of Exposure – becomes CORE Reference Section 10.6 – Extent of Exposure – new Study Subjects, Section 10 (Remainder of Section 12 renumbered accordingly; some additional granularity)
12.2.4 – Listing of Adverse Events by Patient	Not included
12.5 – Vital Signs, Physical Findings, and Other Observations Related to Safety	Becomes Section 12.4 due to renumbering (see above), with new granularity: 12.4.1 – Vital Signs 12.4.2 – Physical Examination Findings 12.4.3 – Other Observations Related to Safety
13 – Discussion and Overall Conclusions	New granularity: 13.1 – Discussion 13.2 – Conclusions
Annexes	Annexes I, IIIa, IIIb, IVa, IVb, and VII adapted and moved into the document body

In short, writers must create CSRs that support heterogeneous study design and cover all emergent content requirements, including public disclosure requirements. ICH E3 and the 2012 Q&A allow flexibility in CSR structuring to suit individual study design. Without a common approach, designing a logical CSR framework for individual studies inevitably results in variable report structures.

CORE Reference is an open-access "user manual to help medical writers navigate relevant guidelines as they create CSR content relevant for today's studies" (5). It is not a template; rather, it presents the focused guidance-required content with other value-added insights, and organises it all into a logical presentational sequence. CORE Reference additionally suggests intelligent anonymisation approaches that will minimise redaction requirement in the publicly disclosed CSR, and pinpoints these within individual CSR suggested sections. In focusing on content and providing suggested common structure, CORE Reference facilitates a content-driven document that is as disclosure-ready as possible. With sufficient uptake, it has the potential to drive standardisation of CSR writing across the industry.

Collateral impacts on the overall drug licensure process from efficiencies gained on individual CSR structural planning and content considerations should positively impact time to market and development costs. 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 (7). Indeed, CORE Reference end users (including CROs and pharma) are beginning to report on the utility of CORE Reference to develop their existing CSR templates. The website supports sharing of disclosure feedback received from the EMA, and this will be fed back into the project to provide industry-wide insight on how best to make each CSR meet the EMA's expectations.

Some four 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 – effective from 18 January 2017 – which mandates posting of clinical trial results information on CT.gov (8). 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 will add tangible value in managing registry postings alongside the writing of CSR results content.

Conclusion

In an industry crying out for standardisation of its documents, these two valuable tools will help streamline the production of two essential documents, the CSP and the CSR. Although in some quarters they may not be seen as perfect – because they break with long held convention and culture – if we can overcome personal preferences and aspire to a higher goal of true standardisation, it could simplify processes, reduce the cost of developing drugs and accelerate getting them to market. This would be real progress that benefits patients.

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References

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3. Visit: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf
4. Visit: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf
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About the authors

Sam Hamilton is a postdoctoral virologist and director of her UK-based consultancy, Sam Hamilton Medical Writing Services. With 22 years of experience in clinical and medical writing roles in the pharma industry, she has written numerous clinical-regulatory document types for all phases of studies and all genres of client. Sam was European Medical Writers Association (EMWA) president, serving two years (2014-2016) on the Executive Committee and is Chair of the CORE Reference project.

Email: sam@samhamiltonmwservices.co.uk

After receiving her PhD in Developmental Neurobiology, **Julia Forjanic Klapproth** started her career as a medical writer in the regulatory group at Hoechst Marion Roussel (later Sanofi) in 1997. Since then, she has been president of the European Medical Writers Association twice. In 2002, Julia co-founded Trilogy Writing & Consulting Ltd, a company that specialises in providing regulatory medical writing. In addition to managing the company as Senior Partner, she writes a wide array of clinical documents including study protocols, study reports, and the clinical parts of CTD submission dossiers.

Email: julia@trilogywriting.com