A new standard for medical writing

Discrepancies in the ways in which the documentation for clinical drug development is structured and presented have hampered understanding and progress for decades. Medical writing consultant **Sam Hamilton** and Trilogy Writing & Consulting co-founder **Julia Forjanic Klapproth** discuss the ways in which a unified approach will benefit the industry and patients alike.

The pharmaceutical industry is highly regulated, with much standardisation. However, documents produced during drug development reflect broad variations on a theme. This is because, despite the array of guidelines describing what these documents should contain (those of the International Council for Harmonisation [ICH] and from local regulatory bodies), there is relatively little prescriptive advice on how to present information consistently. Of course, medicines for different therapeutic areas often have particular content requirements that differentiate them from other therapeutic areas.

a similar way. That means regulatory reviewers receive numerous documents that present information in different ways. This does not contribute to 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. Yet, the reviewer must assess if each new drug would be a valuable addition to the existing armamentarium of medicines. Imagine if every report the reviewer received had the same structure and layout, with standard information in just one, consistent place. This would simplify the review task enormously, and improve transparency, making it immediately apparent if information was missing, or incomplete. The time saved in developing documents would be extensive, as writing teams dispense with discussing options for the structure of the standard elements of a particular document.

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Nonetheless, the ultimate goal is to describe basic concepts for every drug: does it work, and are there any safety concerns that might outweigh its beneficial effect?

Using documents in the clinical drug development arena as an example, the basic ideas behind a protocol, or a study report, are the same, regardless of the type of drug being developed. A protocol must give details of how, what, why and when the activities in a study will be conducted. A study report must explain the data collected in that study.

The ICH guidelines help to ensure that the same types of information are included in these documents, but they do not guarantee information is presented in

Fit for purpose

In the last 12 months, two initiatives have come to fruition that will help streamline the writing of protocols and study reports. The first is the new protocol template issued by TransCelerate. The TransCelerate group is a collaboration between industry stakeholders and regulators intended to produce a definitive template for the clinical study protocol (CSP), regardless of the 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 or in the investigational plan section? Where should details of the various parties involved in performing the clinical study be: 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 be shortened.

At a minimum, TransCelerate 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 precrafted text proposals for many sections will be common across CSPs. Ultimately, industry can save the time spent pondering redundancies and instead focus on study-specific content. ››

Sam Hamilton
Sam Hamilton is a postdoctoral virologist; director of her UK-based consultancy, Sam Hamilton Medical Writing Services; and chair of the CORE Reference project. With 22 years’ experience in clinical and medical writing roles, she has written numerous CSRs for all phases of studies and all genres of client.

Julia Forjanic Klapproth
Julia Forjanic Klapproth co-founded Trilogy Writing & Consulting, a company specialised 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.

Co-author and 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 more efficient study performance.

CORE value

Another new tool, released in May 2016 for clinical study reports (CSRs), is CORE Reference, which is designed to streamline the way CSRs are structured and populated. The international basis for content is laid out in the 1995 ICH regulatory guidance document ICH E3 on the structure and content of CSRs, and the 2012 ICH E3 supplementary questions and answers (Q&A). 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.

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The ever-growing regulatory guidelines 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 European Union, has a profound effect on the way that CSRs are written. European Medicines Agency (EMA) guidance on preparing clinical data for disclosure explains that, because redaction alone will "decrease clinical utility of the data compared with other techniques", it strongly encourages the move towards proactive anonymisation techniques. The impacts on the CSR are multiple and complex, and lessons will be learned as CSRs are disclosed.

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". CORE Reference 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 in 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 pharmaceutical industry.

Final analysis

Collateral impacts on the overall drug licensure process from efficiencies gained on individual CSR structural planning and content considerations, should positively affect time-to-market and development costs. Of course, any resource can only remain relevant if it is updated whenever necessary. This is a stated aim for CORE Reference. Indeed, CORE Reference users (including CROs and pharma) are beginning to report on the utility of CORE Reference to develop their existing CSR templates. The website (www.core-reference.org) supports sharing of disclosure feedback received from EMA and this will be fed back into the project to provide industry-wide insight on how best to make each CSR meet EMA expectations.

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 18 January 2017, which mandates posting of clinical trial results information in CT.gov. 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.

Overall, in an industry crying out for standardisation of its documents, these two valuable tools will streamline the production of a pair of 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 standardisation, it could simplify processes, reducing the cost of developing drugs and accelerate them to market. This would be real progress that benefits patients. ■