Regulatory Public Disclosure

Editorial

In the world of regulatory public disclosure (RPD) things rarely stay the same for long. This regular RPD section in *Medical Writing* and EMWA's RPD SIG help you keep up.

On June 26, 2019, the FDA concluded the recruitment phase of its clinical data summary pilot programme in which one sponsoring pharmaceutical company voluntarily participated. The FDA published a Federal Register notice (Docket No. FDA-2019-N-2012) seeking feedback on the pilot, the comment period for which closed on August 26, 2019. The FDA solicited feedback through a series of stakeholder questions designed to gather insight into potential benefits or risks, resource requirements, and challenges of the FDA publicly releasing a limited number of sections from certain CSRs at the time of marketing approval. The FDA also released a new integrated template that will be used to document the FDA's review of new drug applications and efficacy supplements. The same Federal Register notice sought public comment on the new integrated template. Art Gertel (CORE Reference Strategist) and I submitted our comments in July 2019. This important development is of interest to our professional community because this opens a potentially new and alternative pathway for public disclosure of clinical information to that of the publication of clinical study reports (CSRs) and clinical summary documents that we have to date seen from the EMA and Health Canada. (See Status updates from regulatory regions box for links.)

EMA continues to hold clinical data publication activities. An EMA Management Board meeting is planned in October 2019 to review the situation, but as these activities are not listed as 2019 priorities, I expect that there will be little, if any, movement.

On a more positive note, EMA's improved methodology for the IT system – the Clinical Trials Information System (CTIS) – that will enable the EU's Clinical Trial Regulation to come into force, will hopefully lead to improved delivery. Member states and stakeholders (including business experts) are now directly engaged in the development of CTIS to ensure that their expectations are taken into account. This means that business expert representatives may continuously review, select, and verify CTIS functionalities (See Status updates from the regulatory regions box for links)

This issue's RPD feature article comes from Vivien Fagan. Viv tells us about her transition from the field of dedicated regulatory medical writing into the world of clinical trials disclosure within a global clinical research organisation environment and how she melds the two to ensure disclosure-readiness from the outset. Viv's article includes some great tips on gaining efficiencies from results reporting through to summary results posting (Clinical trial disclosure: Perspective from a medical writer for a contract research organisation, p. 52).

Clarity and Openness in Reporting: E3-based (CORE) Reference, developed by the Budapest Working Group (BWG), a partnership of AMWA and EMWA, is a user manual designed to help medical writers navigate relevant guidelines as they create clinical study report (CSR) content. CORE Reference was one of two principal sources used by TransCelerate BioPharma Inc., an alliance of biopharma companies, in the development of its CSR Template released in November 2018. A new CORE Reference open access article, was published in August 2019 in the BioMed Central journal, *Research Integrity and Peer Review*.

The publication is available at https://doi.org/10.1186/s41073-019-0075-5. Key resources from this publication are posted on the CORE Reference website and are directly accessible via the links in the box below. To whet your appetite, we also reproduce here, with permission, the abstract from the original *Research Integrity and Peer Review* article.

Kind regards, Sam

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Abstract from:

Critical Review of the TransCelerate Template for Clinical Study Reports (CSRs) and Publication of Version 2 of the CORE Reference (Clarity and Openness in Reporting: E3-based) Terminology Table

Hamilton S, Bernstein AB, Blakey G, Fagan V, Farrow T, Jordan D, Seiler W, Gertel A. on behalf of the Budapest Working Group

Background

CORE (Clarity and Openness in Reporting: E3-based) Reference (released May 2016 by the European Medical Writers Association [EMWA] and the American Medical Writers Association [AMWA]) is a complete and authoritative open-access user's guide to support the authoring of clinical study reports (CSRs) for current industry-standard-design interventional studies. CORE Reference is a content guidance resource and is not a CSR template.

TransCelerate Biopharma Inc., an alliance of biopharmaceutical companies, released a CSR template in November 2018 and recognised CORE Reference as one of two principal sources used in its development.

Methods

The regulatory medical writing and statistical professionals who developed CORE Reference conducted a critical review of the TransCelerate CSR template. We summarise our major findings and recommendations in this communication. We also re-examined and edited the Version 1 CORE Reference Terminology Table that we first published in 2016, and we present this as Version 2 in this communication.

Results

Our major critical review findings indicate that opportunities remain to refine the CSR template structure and instructional text, enhance content clarity, add web links to referenced guidance documents, improve transparency to support the broad readership of CSRs, and develop supporting resources.

The CORE Reference "Terminology Table" Version 2 includes estimand as a defined term and an adaptation of the original 'worked study example' to incorporate the recently evolved concept of "estimands".

Conclusions

As TransCelerate's CSR template represents an important milestone in authoring CSRs, we offer CSR authors advice and recommendations on its use, similarities, and differences with CORE Reference and advise them to consider shared interpretations between the two.

Registration

CORE Reference is registered with the EQUATOR Network. The TransCelerate CSR template is not registered with any external organisation to the knowledge of the authors of this paper.

Critical Review of the TransCelerate Template for Clinical Study Reports (CSRs) and Publication of Version 2 of the CORE Reference (Clarity and Openness in Reporting: E3-based) Terminology Table: http://dx.doi.org/10.1186/s41073-019-0075-5

Status updates – from regulatory regions

Europe

1. Priority goals for EMA in 2019 (https://www.ema.europa.eu/en/documents/work-programme/ema-activities-other-highest-priority-activities-category-1-activities-will-continue-2019-annex-1_en.pdf); EMA guideline development and clinical trial data publication on hold (https://www.ema. europa.eu/en/about-us/united-kingdoms-withdrawal-european-union-brexit).
2. CTIS project methodology updated in June 2019 to engage stakeholder input: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation.
3. EU guidance documents applying to clinical trials are described in the Clinical Trials Regulation (EU No. 536/2014). A draft Q & A document dated June 2019 has been released and submitted for discussion to the Expert Group on Clinical Trials. Some sections of the Q&A are incomplete and we can therefore expect this document to be updated. There is a lot of information in the Q&A, as we might expect – do note Section 6 "Submission of Clinical Trial Results" (https://ec.europa.euhealth/sites/health/files/files/eudralex/vol-10/regulation 5362014_qa_en.pdf).
4. Reporting of clinical trial results in EudraCT is the direct responsibility of sponsors. The EMA and the Heads of Medicines Agencies have issued a joint letter to remind sponsors of their responsibilities. They particularly mention underreporting by non-commercial sponsors and provide links to resources that all stakeholders may find useful in meeting their reporting obligations. This July 3, 2019, joint letter (https://www.ema.europa.eu/en/documents/other/joint-letter-european-commission-ema-hma-stakeholders-regarding-requirements-provide-results_en.pdf) and this press release (https://www.ema.europa.eu/en/news/call-all-sponsors-publish-clinical-trial-results-eu-database?mkt_tok=ey) are posted on the EMA's Clinical Trials in Human Medicines page (https://www.ema.europa.eu/en/ human-regulatory/research-development/clinical-trials-human-medicines).

United Kingdom

5. Further detailed guidance published Sept 2019 (https://www.gov.uk/government/publications/further-guidance-note-on-the-regulation-of-medicines-medical-devices-and-clinical-trials-if-theres-no-brexit-deal) includes a major update on all aspects of medicines and devices regulation in the UK in the event of a no-deal Brexit. See Section 3 "Clinical trials of Investigational Medicinal Products" for details relevant to the clinical trials community.
   Register here to make MHRA submissions: https://www.gov.uk/guidance/making-submissions-to-the-mhra-in-a-no-deal-scenario?utm_source=8f1e190e-4364-43e3-b35a-4201a261b4c6&utm_medium=email&utm_campaign=govuk-notifications&utm_content=daily

United States

6. The FDA concluded the recruitment phase of its clinical data summary pilot programme (https://www.fda.gov/drugs/development-approval-process-drugs/clinical-data-summary-pilot-program) and published a Federal Register notice seeking feedback on the pilot and a new integrated template (https://www.federalregister.gov/documents/2019/06/27/2019-13751/new-drugs-regulatory-program-modernization-improving-approval-package-documentation-and). The applicable Docket No. FDA-2019-N-2012 for "New Drugs Regulatory Program Modernisation: Improving Approval Package Documentation and Communication", including the background documents and comments received, is at: https://www.regulations.gov. Just insert the docket number into the search box and follow the prompts. Comments from Sam Hamilton and Art Gertel are also available at https://www.core-reference.org/media/1053/docket-fda-2019-n-2012_answers-to-fda-qs_sh-and-ag_150719.pdf.

Eastern Mediterranean

7. On July 25, 2019, the Lebanese Clinical Trials Registry (LBCTR) became a member of the Primary Registry Network of ICTRP. LBCTR is also becoming a data provider and trials registered with LBCTR will be added to the ICTRP database. LBCTR was established by the Lebanese Ministry of Public Health with the support of the WHO Lebanon office and the WHO Eastern Mediteranean Regional Office (EMRO) IT team. This new registry will contribute to research transparency in the EMRO region and will ensure the registration of all clinical trials conducted in Lebanon (https://www.who.int/ictrp/news/en/).

… from the journals

8. Miller J, et al. Sharing of clinical trial data and results reporting practices among large pharmaceutical companies: cross sectional descriptive study and pilot of a tool to improve company practices. BMJ 2019; 366:l4127 (http://dx.doi.org/10.1136/bmj.l4127) shows that "…Despite noteworthy commitments by some companies to share participant level trial data and a willingness by others to improve their policies, many companies still have substantial room for improvement."
9. Evuarherhe O, et al. Professional medical writing support and the quality, ethics and timeliness of clinical trial reporting: a systematic review. Research Integrity and Peer Review volume 4, Article number: 14 (2019) (https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-019-0073-7) describes the relationship between professional medical writing support for authoring CSRs, and the quality, ethics and timeliness of publications reporting clinical trials.
10. Clinical trial registry reporting: a transparent solution needed (https://doi.org/10.1016/S1470-2045(19)30350-X) is a Lancet editorial that highlights the shortfall in trial registry results reporting by universities in Europe. University triallists are encouraged to take the lead and make the necessary uploads, and it is suggested that clinical trial registries could send out automated email reminders.
11. Rocher L, et al. Estimating the success of re-identifications in incomplete datasets using generative models. Nature Communications, 2019; 10 (1) (https://www.nature.com/articles/s41467-019-10933-3) shows that allowing data to be used, to train artificial intelligence algorithms, for example is risk laden. This new research shows that once bought, the data can often be reverse engineered using machine learning to re-identify individuals, despite the anonymisation techniques.

CORE Reference

- Hamilton S, Bernstein AB, Blakey B, et al. Critical Review of the TransCelerate Template for Clinical Study Reports (CSRs) and Publication of Version 2 of the CORE Reference (Clarity and Openness in Reporting: E3-based) Terminology Table. *Research Integrity and Peer Review*. https://doi.org/10.1186/s41073-019-0075-5.
- CORE Reference (available for download from http://www.core-reference.org/core-reference/) identifies each point in an ICH E3-compliant CSR where anonymisation considerations should apply. Downloads stand at 22,500+ (Sept 2019)
- CORE Reference News Summaries: https://www.core-reference.org/news-summaries and "real time" updates: http://www.core-reference.org/subscribe

Resources

1. The EMA's Scientific Advice Working Party released "Draft qualification opinion of clinically interpretable treatment effect measures based on recurrent event endpoints that allow for efficient statistical analyses" – which is relevant for development of estimands, i.e., clinically interpretable treatment effect measures (https://www.ema.europa.eu/en/documents/scientific-guideline/draft-qualification-opinion-clinically-interpretable-treatment-effect-measures-based-recurrent-event_en.pdf). Development of medicines is becoming increasingly estimand-based, and as we all try to better understand this developing field, I urge you share this opinion with your statistical colleagues. See Table 2 at https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-019-0075-5/tables/2 for incorporation of estimand into the original CORE Reference Terminology Table worked example
2. The Center for Biomedical Research Transparency aims to increase transparency in biomedical research reporting. This *ISMPP Newsletter* reports the content that was presented in a free-to-attend meeting in the EU in May 2019 (https://ismpp-newsletter.com/2019/06/18/ introducing- cbmrt-its-transparency-initiatives-and-ambassador-network/). More of these meetings are planned for the EU and US. Although the topics of interest relate predominantly to publications transparency, (and less so to clinical data transparency in the clinical trials industry), free meetings like this where there is overlap of these areas may be of interest.
3. EMWA RPD SIG members' page: https://www.emwa.org/members/special-interest-groups/regulatory-public-disclosure-sig/ Subpage for disclosure-related regulatory news updates: https://www.emwa.org/members/special-interest-groups/regulatory-public- disclosure-sigregulatory-news-emwa-newsblast/.