Regulatory Matters

Symbiotic relationships in medical writing and regulatory operations

SECTION EDITOR

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A symbiotic relationship is an "intimate interaction between two or more species, which may or may not be beneficial to either".[1] We can think of the bee and flower relationship. The flower provides the bee with nectar, while the bee provides pollination. Each entity or group in the relationship benefits from knowing or interacting with one another; they need each other to survive and prosper.

The biopharma industry is a complex ecosystem with myriad interdependencies. The interconnected organisms in this ecosystem experience many moving parts within their respective operations, including shifting priorities/timelines, process changes, system upgrades, and internal/external requirements, just to name a few. This is evident on the micro- and macrocosm levels. Communication and collaborative interaction are the keys to a successful relationship, especially between a medical writing department and a document publishing/content management centre of excellence in regulatory operations. Creating a symbiotic relationship involves trust, collaboration, innovation, risk, people, and leadership.[2]

Trust: *Do you trust the expertise? Are you willing to share insights?*
Ensure expertise is in the right areas. Identify skills for each group and/or create subject matter experts. Ensure accountability. The focus of a document publishing and content management group is to provide documents that meet the electronic submission requirements. The group members are Word and PDF experts who focus on formatting, publishing, quality control, and submission readiness. We interact with medical writers, statisticians, and downstream submission publishers. It is important not to make one group responsible for work that can be done by experts in another group. Each group can share and leverage their knowledge and expertise more broadly.

Collaboration: *Do you work cross-functionally? Do different groups come together?*
Promote the interaction of group members. Ensure all stakeholders are considered in the end-to-end timeline. Encourage representatives of the ecosystem to meet regularly and consult actively with project teams. The groups should have a general understanding of each other's role. Last-minute changes are known to happen in the clinical and regulatory space, and being able to identify the correct point of contact can save valuable time when compiling a submission.

Innovation: *Do you have processes to capture innovation? Can you learn to repeat them?*
Plan for success. Keep everyone up to date on process and procedure changes. Share across groups what processes work and what doesn't work. Capture the best practices in order to repeat the desired outcome, then promote consistency. Part of my role is to meet with medical writers on a regular basis. We focus on quality metrics, concerns, issues, and processes. It is important that both groups participate. We are able to capture patterns, good and bad, and then implement a solution and/or perpetuate best practices.

Risk: *Can you afford to make the change? Does the benefit outweigh the risk?*
As mentioned before, our organisations have many moving parts and they need to synchronise across departmental boundaries. When a process or system requires an update in one area, we have to take time to investigate the impact within the ecosystem. If there is a symbiotic relationship, identifying the gaps to align the end-to-end process can become systematic and create opportunities for improvement across the organisations.

People and leadership: *Do we have the people involved to develop opportunity?*
Select people who can provide leadership. The ecosystem needs leaders who can prioritise projects or tasks then create a strategy and

execute it. Strategy is simple – focus on the activity. Execution is complex and takes time to perfect. "But without direction, simple clarity on strategy, execution is merely hysterical activity confusing effectiveness with activity".[3]

The points above allow for knowledge transfer, gap identification, project prioritisation, and process and procedure consistency. The end goal is to ensure submission-ready components are delivered. All groups must interact in order to successfully meet deadlines.

The benefits of a symbiotic relationship can improve performance, increase effectiveness, expand workload, and outweigh risk with reward. Remember the bee and flower – only the flowers that interact with the bee prosper. The investment in the relationship determines the outcome; you get what you put in.

References

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3. Smith I. The symbiotic relationship in business – complexity & simplicity. [Internet]. The Portfolio Partnership. 11 Dec 2012 [cited 4 Oct 2018]. Available from: http://portfoliopartnership.com/the-symbiotic-relationship-in-business-complexity-simplicity/.

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Regulatory Public Disclosure

Editorial

Regulatory public disclosure (RPD) is a fast-evolving area. This regular section of *Medical Writing* and EMWA's RPD Special Interest Group (SIG) can help you develop your understanding and maintain your knowledge. The RPD SIG members' page: https://www.emwa.org/members/special-interest-groups/regulatory-public-disclosure-sig/ has a new subpage for disclosure-related regulatory news updates: https://www.emwa.org/members/special-interest-groups/regulatory-public-disclosure-sig/regulatory-news-emwa-newsblast/.

In this issue's open-access RPD feature article (Meister R, page 57), a US-based colleague describes the historical background, development, and current status of the plain language summary. Ro raises awareness of the suitability of professional medical writers in conveying clinical trial outcomes to trial participants – and the wider general public – because we understand the clinical trial process and the importance of clinical trial transparency and disclosure, and because we can convey complex information with clarity. Writing plain language summaries is surely a work opportunity not to be missed.

Our short article this quarter is a slick "information harnessing" piece by Kathy B. Thomas, freelance consultant and regular speaker at EMWA conferences. Kathy generously shares her "go-to" internet sites hosting key clinical trial disclosure-related resources. Keep it handy for reference purposes.

Awareness of the importance of clinical trial disclosure is growing, as evidenced by increasing numbers of companies seeking to establish dedicated business units to uphold this new discipline. If you are involved in this swathe of development, and would like to write about it, do please contact me. As ever, send in ideas for articles, tips, and points to help us all hone our disclosure writing. I will continue to information share via this regular *Medical Writing* section, through www.core-reference.org emails (sign up at: http://www.core-reference.org/subscribe), and through EMWA News Blasts.

Kind regards, Sam

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Clinical trial disclosure:

Useful Internet sites for trial sponsors and database users

Clinical trial disclosure is a well-known topic to those performing and reporting clinical trials. Registration of new clinical trials and disclosure of results for completed clinical trials in public internet databases is now generally accepted by trial sponsors. Publications on the topic appear frequently in high-ranking journals, blogs, specialist newsletters, and general newspapers. Such publications report new or updated legal requirements, metrics of the reported (or *not reported* information), and on the implications of the transparency and disclosure requirements for sponsors of clinical trials.

Information on the clinical trials can be found in internet databases (most freely accessible without any subscription). The databases are global, regional, or national, which makes the timely management, updating, and content consistency a challenge for those implementing and coordinating the database entries. Countries of the EU and of the European Economic Area (EEA: Iceland, Liechtenstein, and Norway) as well as the US are particularly active in advocating and enforcing clinical trial disclosure. Additionally, some further 40 countries worldwide have national disclosure obligations; certain countries have more than one relevant registry or database that needs attention.

Entry of information into the databases is based initially on the "Clinical trial protocol" – this constitutes the "registration" of a *new* clinical trial and later on, after the trial has been *completed* (… or prematurely ended) the database entry is based on "Clinical trial report" – a procedure that

represents the disclosure of clinical trial results (also referred to as posting of results).

USA

Clinical trials that are performed under the US jurisdiction and are applicable for disclosure are governed by the FDA Amendment Act of 2007 Section 801 (often referred to as FDAAA 801 statute), and which was expanded by the Final Rule making in 2016. The requirements of the statute, expanded by the Final Rule, are fully effective from 18 January 2017. The database associated with FDAAA 801 expanded by the Final Rule, is the ClinicalTrials.gov www.clinicaltrials.gov, which is maintained and managed by the National Institutes of Health (NIH), National Library of Medicine.

EU/EEA

For trials that are under the legal authority of the EU/EEA, the relevant law is the Regulation EU No. 536/2014, which is to replace the existing laws – namely the Clinical Trials Directive 2001/20/EC and the Paediatric Regulation (EC) No. 1901/2006. Regulation EU No. 536/2014 is intrinsically connected to a *functional* single EU portal and database.

Although Regulation EU No. 536/2014 came into force in 2014, its provisions will not take effect before mid 2020. This delay is due to complex technical demands of the single EU portal and database which will store and facilitate information flow between the EMA and EU/EEA member states. During the interim period (while the single portal and database are being developed, tested, and validated), the current applicable disclosure laws remain in force, i.e. the Clinical Trials Directive 2001/ 20/EC and the Paediatric Regulation (EC) No. 1901/2006. Consequently, the database that contains registration and results of clinical trials remains the www.clinicaltrialsregister.eu.

Despite the delay in the effective date for the Regulation EU No. 536/2014, sponsors of clinical trials in the EU/EEA are urged to invest time and resources to educate themselves and understand the requirements of Regulation EU No. 536/2014, assign staff and set up internally tested standard operating procedures, so as to be ready for the effective date.

Trial trackers

For the two ICH world regions that are the subject of this article, the databases are being monitored for timely entry of results of completed clinical trials. Outcome of such monitoring is performed with the so-called "trial trackers" and the findings are public through live informatics tools that monitor compliance of the FDAAA 801/Final Rule-relevant trials in the NIH database (http://fdaaa.trialstracker.net/) and of trials in the EU/EEA, in the EudraCT database (http://eu.trialstracker.net/).

Facilitating learning and understanding of the clinical trial disclosure topic

The information presented in Table 1 below is intended to facilitate learning and understanding of the clinical trial disclosure topic. The Table contains information on the definitions of elements that are required for the registration and results disclosure of new trials or completed trials, respectively, in ClinicalTrials.gov and/or in the clinical trials register (EudraCT). As new topics are raised, the information on the Internet sites is updated.

The Internet sites with "frequently asked questions" (FAQs) provide valuable information on items raised by trial sponsors and database users. Other sites contain information about the procedures of how to enter the data into the database fields, definitions of fields, interpretations of the relevant laws or requirements from other influential bodies or organisations (such as the International Committee of Medical Journal Editors, the World Medical Association that developed the Declaration of Helsinki, and the World Health Organization).

Further information and references

Detailed information on the topic of clinical trial disclosure is available in the recent publications and references within:

- Thomas Kathy B. Clinical trial disclosure and transparency: Regulation EU No. 536/2014. Public disclosure at the clinical trial level. Medical Writing 27(2):7–17, 2018 http://journal.emwa.org/public-disclosure/clinical-trial-disclosure-and-transparency/[accessed 2018 September].
- Thomas KB. Clinical trial disclosure and transparency: ongoing developments on the need to disclose clinical data. In Medical writing the backbone of clinical development. International Clinical Trials. pp 63-70, 2017. http://edition.pagesuite-professional.co.uk/launch.aspx?eid=f6b80f6a-ddd6-4705-bc9a-8af003f96adb [accessed 2018 September].
- Thomas KB. Clinical Trial Disclosure and Transparency: The Medical Writer's Perspective; in Thomas KB, Reeves A, (eds): EMWA Symposium. EMWA, 2014, pp 6–17. http://www.emwa.org/Documents/Transparency%20Symposium%20Budapest%20Final.pdf [accessed 2018 September].

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Table 1: Clinical trial disclosure: Useful sites for clinical trial sponsors and database users

US (ClinicalTrials.gov database) www.clinicaltrials.gov

FAQ NIH site	https://clinicaltrials.gov/ct2/manage-recs/faq
Data elements and study registration tequirements	https://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf Includes requirements from: WHO, ICMJE, and NIH
ClinicalTrials.gov **Protocol Registration** Data Element Definitions for Interventional and Observational Studies.	https://prsinfo.clinicaltrials.gov/definitions.html This site also contains information on individual participant data sharing (a requirement of ICMJE).
ClinicalTrials.gov **Results Data Element** Definitions for Interventional and Observational Studies	https://prsinfo.clinicaltrials.gov/results_definitions.html
Trial tracker	http://fdaaa.trialstracker.net/

European Medicines Agency (EMA) www.clinicaltrialsregister.eu

FAQ EMA site	https://eudract.ema.europa.eu/docs/guidance/EudraCT%20FAQ_for%20publication.pdf
EudraCT Database	https://eudract.ema.europa.eu/help/Default.htm site also includes links to: ● Protocol-related information ● Result-related information
Clinical Trials Regulation (EU) NO 536/2014 Q&A (Version 1.0 April 2018)	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
Community clinical trial public home page	https://eudract.ema.europa.eu/ site also includes links to: ● Protocol-related documentation ● Result-related documentation ● Training tutorials on results entry into database ● Statistics ● Technical aspects
Trial tracker	http://eu.trialstracker.net/

EMA=European Medicines Agency; EudraCT= European Union Drug Regulating Authorities Clinical Trials; ICMJE=International Committee of Medical Journal Editors; NIH=National Institute of Health; WHO=World Health Organization

CORE Reference

- Read the CORE Reference Press Release on the TransCelerate CSR template at: https://www.core-reference.org/news-summaries/core-reference-statement-on-transcelerate-csr-template/
- CORE Reference (available for download from http://www.core-reference.org/core-reference/) identifies each point in an ICH E3-compliant clinical study report where anonymisation considerations should apply. Downloads stand at 15,000+ (December 2018).
- Sign up for emails via: http://www.core-reference.org/subscribe.
- CORE Reference-related updates are now available in Japanese on a dedicated blog (https://clinos.com/blog/category/core-reference/). Thank you to Yukie Uchiyama (responsible for Japanese writing of the blog) and Hiroko Ebina (responsible for quality assurance of the blog) for making this initiative possible. Note: The opinions expressed in Yukie Uchiyama's blog, and the interpretations of CORE Reference are solely those of the blogger, and are not necessarily those of the CORE Reference authors.

Status updates – from regulatory regions

United States

1. In September 2018, FDA issued draft guidance titled "Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank" (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM607698.pdf) describing FDA thinking on financial penalties against sponsors of clinical trials who do not register and/or submit results information to ClinicalTrials.gov.

2. Clinical study protocols are publicly disclosed documents, making the following September 2018 draft FDA guidance releases on protocol development relevant:

- "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics – Guidance for Industry" (https://www.fda.gov/ucm/groups/ fdagov-public/@fdagov-drugs-gen/documents/document/ucm621817.pdf)
- "Adaptive Designs for Clinical Trials of Drugs and Biologics – Guidance for Industry" (https://www.fda.gov/ucm/groups/fdagov-public@fdagov-drugs-gen/documents/ document/ucm201790 .pdf)

Europe

1. EMA has a new "Clinical data publication" page (https://www.ema.europa.eu/en/ human-regulatory/marketing-authorisation/ clinical-data-publication) that explains that EMA is temporarily suspending clinical data publication until further notice.

This page also includes links to:

- The **"Support for industry on clinical data publication"** page (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication/support-industry-clinical-data-publication) This comprehensive page includes detailed guidance for pharmaceutical companies on requirements to comply with Policy 0070, and also includes downloadable justification table templates.
- **EMA's clinical data website** (https://clinicaldata.ema.europa.eu/web/cdp/home) This page hosts publicly disclosed clinical data.
- The "**External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use**" page (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication/support-industry/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data).

The latest implementation guidance is Revision 4, dated November 9, 2018; (https://www.ema.europa.eu/documents/regulatory-procedural-guideline/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data_en-3.pdf) read the summary of changes at: https://www.ema.europa.eu/documents/other/summary-changes-external-guidance-implementation-european-medicines-agency-policy-publication_en-2.pdf.

2. EMA is compiling a report listing those sponsors on EudraCT who are not compliant with results posting requirements. The report was planned for publication in September 2018 and EMA will be contacting those sponsors individually. This information was communicated directly by an EMA representative at a web meeting of the DIA's Clinical Trial Disclosure Community in mid September 2018.

3. EudraCT Clinical Trials Tracker (http://eu.trialstracker.net) is fully established. This tool is searchable by sponsor and indicates the percentage of reported trials on EudraCT – out of the trials that are due to report.

4. In September 2018, 11 national research funding organisations, backed by the EC and the European Research Council (ERC), announced the launch of "cOAlition S" (https://www.scienceeurope.org/coalition-s/), an initiative to make full and immediate open access to research publications a reality.

By January 1, 2020, the aim is to fulfil this main principle: "By 2020 scientific publications that result from research funded by public grants provided by participating national and European research councils and funding bodies, must be published in compliant open access journals or on compliant open access platforms."

… from the Journals

The 2018 *BMJ* article: "Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource" (https://doi.org/10.1136/bmj.k3218) describes compliance of 50% for results posting on EudraCT over a 1-year period to December 21, 2016. This paper also describes the EudraCT Clinical Trials Tracker (http://eu.trialstracker.net).

Hopkins and colleagues' September 2018 paper "Data sharing from pharmaceutical industry sponsored clinical studies: audit of data availability" (https://doi.org/10.1186/s12916-018-1154-z) assesses whether data sharing policies are facilitating independent researcher access to participant-level data from industry-sponsored trials 2 years after publication of the primary results. The findings show that there remains significant room for improvement; the authors present key issues that have limited data sharing.

Resources

November 2018 TransCelerate assets: New CSR, new SAP, and updated CSP Templates

TransCelerate has released new and updated clinical document templates under their Common Protocol Template resources at: http://www.transceleratebiopharmainc.com/assets/common-protocol-template/

Read the CORE Reference Press Release on the TransCelerate CSR template at: https://www.core-reference.org/news-summaries/core-reference-statement-on-transcelerate-csr-template/

TransCelerate webinar on the Common Protocol Template

A recording of the September 27, 2018, TransCelerate webinar session on their Common Protocol Template, along with a PDF slide deck is available from: https://connect.eventtia.com/en/dmz/4d19/ website

EFPIA-sponsored Data Transparency Conference – Brussels, February 2019

On February 12 and 13, 2019, the ECCRT Data Transparency Conference (http://www.eccrt.com/events/eccrt-data-transparency-conference) on "Demystifying Clinical Data Transparency: Lessons learnt so far' includes speakers from the CORE Reference development team. Programme: http://www.eccrt.com/sites/default/files/eccrt_images/data_transparency_conference_eccrt.pdf