Medical Writing

Clinical trials

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Volume 32 Number 1 | **March 2023**

EMWA EUROPEAN MEDICAL WRITERS ASSOCIATION

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Medical Writing

THIS ISSUE **March 2023** | Volume 32 Number 1

Clinical trials

"This issue of *Medical Writing* is dedicated to the unsung heroes and heroines of clinical trials: medical writing professionals who help make clinical trials happen without visiting a clinic or interacting with a single patient."

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Unsung heroes: The medical writer's role in clinical trials

Every year, the number of clinical trials conducted globally is increasing rapidly (approximately 10,000 annually!). According to the WHO data statistics and analysis, the number of clinical trials conducted from 1999 to 2021 has accumulated to 671,228 clinical trials.[1] As of February 28, 2023, 443,624 clinical trials have been registered on ClinicalTrials.gov.

The medical writer is heavily involved in clinical trials from A to Z and even beyond. Although we are not in the frontline, our role is nevertheless crucial as we develop most of the documents needed for trial start up, conduct, close out, and reporting (see Fig 1). This issue of *Medical Writing* is dedicated to the unsung heroes and heroines of clinical trials, medical writing professionals and scientists who help make clinical trials happen without visiting a clinic or interacting with a single patient.

This issue starts off with a foreword from the European Medicines Agency (EMA) wherein **Morgane Colin de Verdiere** and

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doi: 10.56012/pvjb4577

Catriona Ester of the EMA Medical and Health Information Service give an overview of the implementation of EU Clinical Trials Regulation 536/2014 (EU CTR) and the launch of the Clinical Trial Information System (CTIS).

Clinical trials start with the study protocol and the medical writer is a key stakeholder in its development. Decentralised trials (DCT) came to the forefront during the pandemic. **Jonathan Mackinnon** describes tools and strategies for DCT protocols. **Kishor Patil, Chandra Kumar,** and **Siu-Long Yao** provide practical tips on the peer review process of protocols.

Once the protocol is written, reviewed, and finalised, a clinical trial application (CTA) can be submitted. As of Jan 31, 2023, CTAs are centrally submitted through the CTIS. **Ivana Turek** gives us a short overview of the differences in CTA requirements between the old (Clinical Trial Directive) and the new (EU CTR) legislations.

Before study start, protocols are registered in a clinical trial registry and details are made available to the public. Under the EU CTR, a protocol synopsis for the lay person is recommended. **Lisa Chamberlain James** looks at this new requirement and points out the challenges and opportunities.

Titles of clinical trials, too, should be understandable to the lay audience. **Leonie Leithold, Clive Brown, Julia A. Hild, and Thomas Schindler** performed a systematic analysis of the titles of clinical trials and identified opportunities for improvement.

Clinical trials revolve around the common theme of evaluating the efficacy and safety of medical therapies but they may differ depending on disease, patient population, and geography.

Zuo Yen Lee walks us through the complexity of oncology trials while **Sarah Milner, Andrew Kusmierczyk, and Julie Taccoen** take on the clinical trial landscape of rare diseases.

In the area of medical devices, trials are called clinical investigations, described by **Beatrix Doerr**, **Shirin Khalili**, and **Joan D'souza**.

And while most of us are familiar with clinical trials in the European Union, it is interesting to hear from **Eugenia Radkova** and **Irina Petrova** about similar rules and requirements of conducting clinical trials in the Eurasian Economic Union.

When the clinical trial closes, a new set of tasks awaits the medical writer. The clinical study report presents the results of clinical trials. **Surayya Taranum** provides a snapchat of the medical writer's role in the development of this milestone document.

EUROPEAN MEDICAL WRITERS ASSOCIATION

Submissions:
For instructions to authors, go to the journal section of EMWA's website (www.journal.emwa.org).
All manuscripts should be submitted to mew@emwa.org.

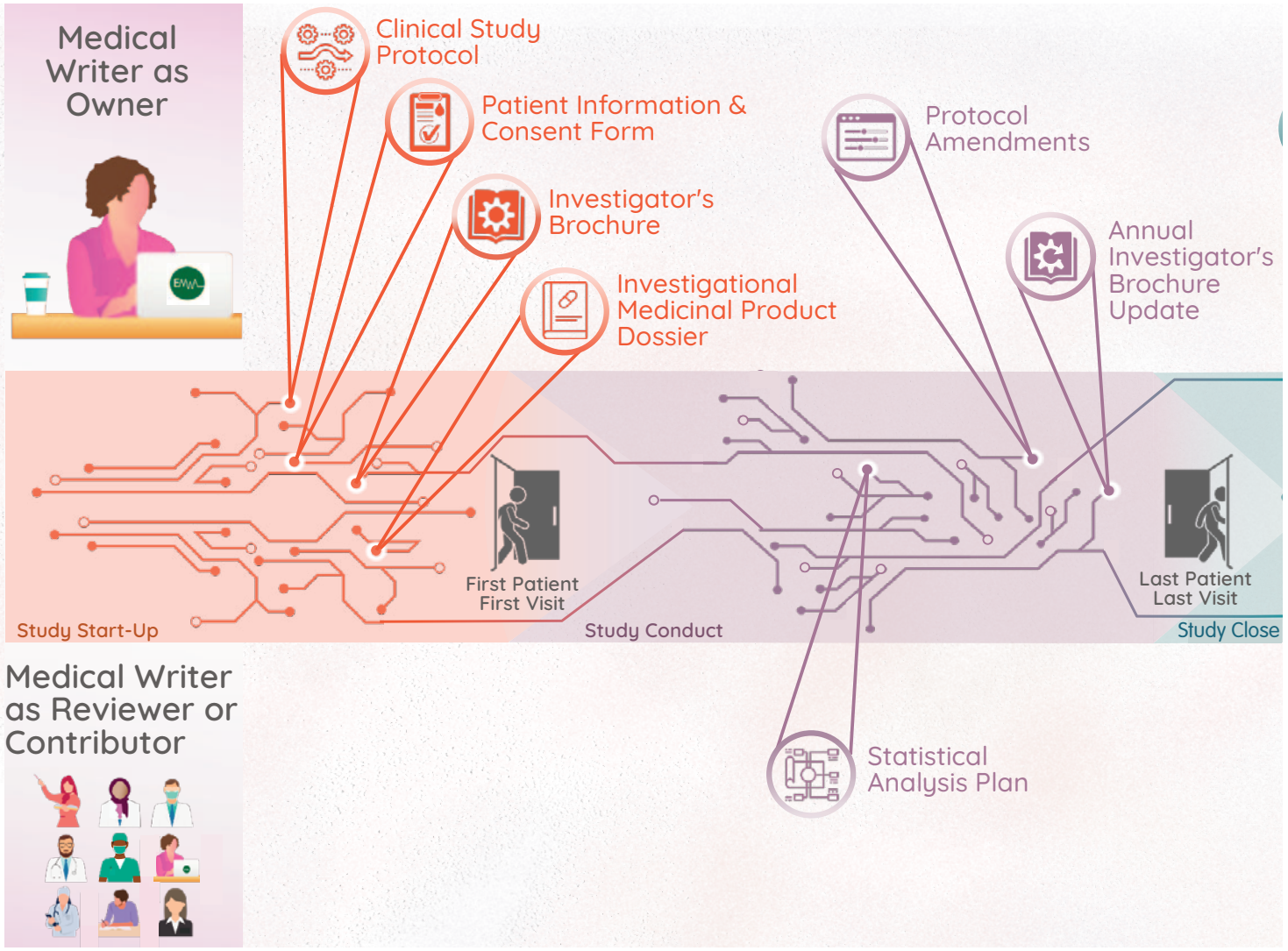

Figure 1

Public disclosure of clinical trial results comes with responsibility to protect personal data. **Tatiana Revenco and Gregory Collet** address the role of medical writers as data processors in protecting patient privacy under the purview of the EU General Data Protection Regulation.

Ambika Subramanian reminds us that medical writers should have a wider perspective when preparing clinical documentation as every document is interconnected, across the different stages of a medicine's lifecycle.

Hope you find this issue as informative as we do!

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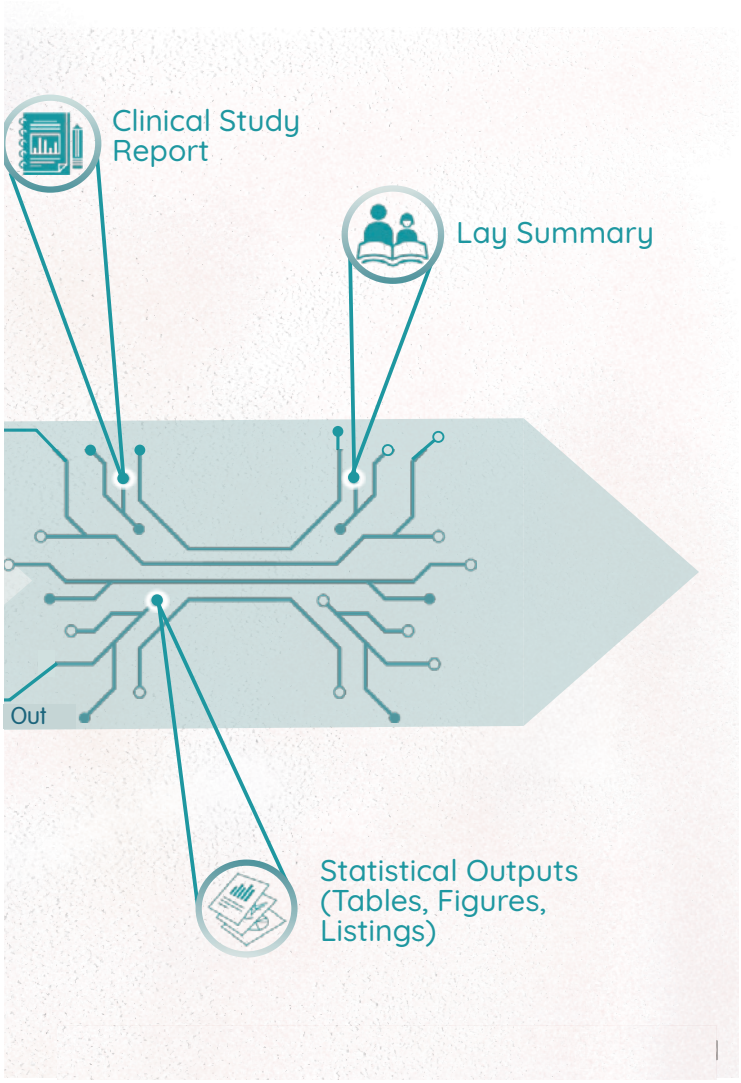
Ivana Turek, PhD, is currently working in the regulatory sciences field for a global pharma company and has been an active EMWA member since May 2021. Her main professional interests are clinical trials, regulatory writing, and market analysis.



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References:

1. WHO Number of clinical trials by year, location, disease, phase, age and sex of trial participants [cited 2023 Jan 20]. Available from: https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-trial-registrations-by-year-location-disease-and-phase-of-development
2. USFDA. Clinical Trial Diversity [cited 2023 Jan 20]. Available from: https://www.fda.gov/consumers/minority-health-and-health-equity/clinical-trial-diversity
3. ICH guideline E8 (R1) on general considerations for clinical studies 1 Dec 2022. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-8-general-considerations-clinical-trials-step-5_en.pdf

President's Message

From scurvy to Covid-19: The role of clinical trials, and medical writing's crucial role in the process

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2022-23
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doi: 10.56012/eoag8863

Dear EMWA friends and colleagues,

The medical writing community is intrinsically involved in regulatory documentation that spans the entire timeline of clinical research – from study protocols and informed consent to clinical study reports and even post-market pharmacovigilance. Hence, it is indeed apposite that the theme of this issue is Clinical Trials.

Medical research has come a long way since James Lind's scurvy trial in the 18th century to the first double-blind randomised controlled trial in 1946 investigating streptomycin in pulmonary tuberculosis. In the present day, clinical trials represent one of the most highly regulated activities of medical research, with an emphasis not only on scientific rationale but also on ethics in human experimentation. Although regulatory agencies, medical professionals, ethics bodies, and trial sponsors each have a role in the planning, design and execution of clinical trials, the key role is the one of the trial volunteers – the lay persons with a certain amount of motivation to get involved in the scientific process. While the Nuremberg Code of 1947 laid the foundations for including informed consent, the ethical principles integral to clinical trial methodology have since been refined to establish the Good Clinical Practice (GCP) guidelines. What this evolution has essentially underpinned is the need to principally bear in mind at all times the safety of the clinical trial volunteer. An informed trial participant is key to the success of a clinical trial, for on it depends participant adherence.

Photo: Wikicommons images0

The last 20 years have witnessed a steady growth in the number of clinical trials conducted worldwide with the most recent estimate from the World Health Organization's International Clinical Trial Registry Platform showing over a half million clinical studies registered worldwide in 2021. Although this is perhaps an unexpectedly large number, it gives a misleading impression that clinical research is spread across all regions of the world homogeneously; the majority of clinical research is conducted in the global north. This in itself does not come as a surprise since the cost and technical expertise required for running clinical trials makes it restrictive to the underdeveloped parts of the world. It is encouraging to note that in the last 10 years or so, various Asian countries are turning into clinical research hubs; currently China, India and the Republic of Korea feature in the top 15 countries by the number of ongoing clinical trials. This benefits clinical research in numerous ways mainly by promoting international collaborations, increasing diversity in the studied population, and speeding up the process. A stellar example of this in action is the rapidity with which Covid-19 vaccines could be investigated and brought to the public, thereby averting a much higher mortality that would have ensued in the absence of the vaccine. Needless to say, the world collectively owes gratitude to the volunteers who participated in these trials. Indeed, the clinical trial process is one where humankind volunteers to benefit others.

Photo: Wikicommons images

Happy reading!

Photo: Freepik

May 11, 2023

at EMWA's 11th Symposium

on the Clinical Trials Regulation EU 536/2014 (EU CTR) and its impact on clinical trials and medical writing and communications.

Expert speakers representing different stakeholders will share their views and insights on the EU CTR, with focus on new requirements and processes, and their impact on functions in medical writing and communications. We will be hearing different perspectives from representatives of:

- European Medicines Agency (EMA)
- European Federation of Pharmaceutical Industries and Associations (EPFIA)
- Pharmaceutical companies as clinical trial sponsors
- Regulatory medical writers and pharmacovigilance writers
- Transparency specialists
- Contract research organisations and medical writing agencies
- Patient advocacy groups
- Publications professionals

The EU Clinical Trials Regulation and its much-anticipated benefits:

Foreword from the European Medicines Agency

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The year 2022 signalled the beginning of a new way of handling clinical trials in Europe, with the implementation of the EU Clinical Trials Regulation 536/2014 (CTR).[1] This eagerly awaited regulation came into application at the end of January 2022 with a three-year transition period. The new regulation will facilitate sponsors' clinical trial applications in the EU, while streamlining the assessment and supervision processes for regulatory authorities. This will make it easier to carry out larger clinical trials in multiple EU member states, which in turn should foster further innovation and research in the EU.

Moving from the old Clinical Trials Directive to the EU CTR is not without challenges and involves far-reaching changes to how medicines developers, EMA, and EU member states operate. During the transition period, EMA is therefore working closely with users to provide training and support and to address technical difficulties. Ultimately, however, the EU CTR should benefit all those involved, especially patients, through increased transparency of clinical trial data and stronger patient involvement.

As part of the new regulation, EMA has developed the Clinical Trials Information System (CTIS), which will replace the EudraCT database and become mandatory for all new clinical trial applications as of January 2023. By January 31, 2025, all ongoing trials approved under the old Clinical Trials Directive will be governed by the new regulation and must have been transitioned to CTIS. CTIS provides a single-entry point for clinical trial sponsors and regulators through which to submit and assess clinical trial data. To make information about each clinical trial more accessible to a wider audience, it also includes a searchable database for healthcare professionals, patients and the general public, available at euclinicaltrials.eu.[2] This database will prospectively contain detailed information on all clinical trials authorised through the system, including their outcomes. With this in mind, sponsors are encouraged to present data in a user-friendly, searchable format.

As part of the continuing drive to better inform and involve patients, sponsors now also need to submit a lay summary, together with the Summary of Clinical Trial Results, within 12 months of the end of most clinical trials. This lay summary should offer patients and the public an unprecedented chance to understand what is going on in medical research, while also allowing sponsors the opportunity to communicate their results in a more harmonised way. This new requirement reflects ongoing efforts to increase transparency and acknowledges the important contribution patients make to the advancement of medical research.

Patient engagement is at the heart of all that EMA does. For many years now, EMA has itself provided lay language summaries of authorised medicines, drafted in consultation with patient representatives. These summaries, known as medicine overviews, are the landing page of any medicine authorised by EMA and include a plain-language explanation of the assessment of the clinical trial data that underpinned EMA's decision. As such, EMA's medical writers know better than most the challenges of writing a summary in lay language. It is a fine balancing act, ensuring that the language is simple, without

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compromising the accuracy of the information provided. As new clinical trials come to a close, the medical writers' community at large will find itself facing similar issues. To support medical writers in preparing and writing a good lay summary, the European Commission has issued guidance on good lay summary practice,[3] which includes recommendations on patient involvement, presenting data, and the use of lay language. Medical writers may also be interested in EMA's medical terms simplifier,[4] a glossary of lay-language terms commonly used in EMA's communications for the public.

EMA is committed to stimulating innovative clinical research in the EU, while also maintaining protection of trial participants, and guaranteeing data robustness and transparency that EU citizens expect. Although very welcome, the greater transparency offered by CTIS and EU CTR requires a stringent approach to protection of personal data and commercially confidential information (CCI). A range of measures have been put in place to ensure this is achieved. Key considerations are outlined in a draft EMA guidance[5] on the protection of personal data and CCI in documents to be published in CTIS. EMA is also closely monitoring the implementation of the CTR within the context of Accelerating Clinical Trials-EU (ACT-EU), an initiative seeking to transform how clinical trials are designed and run, with monthly metric reports on progress.[6]

It is clear that it is more important than ever to empower EU citizens and patients so that they can make informed decisions about their healthcare. These far-reaching changes to the clinical trials regulatory landscape in the EU are important steps towards strengthening patient involvement in clinical trials and boosting their understanding of research and study outcomes. In turn, this will have a positive effect on the overall EU regulatory system for medicines, reinforcing public confidence in authorised medicines and contributing to a more conducive environment for future research.

References

1. European Commission. Regulation EU No 536/2014. Available from: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en
2. Clinical trials in the European Union: Clinical Trial Information System (CTIS). Available from: https://euclinicaltrials.eu/
3. Good Lay Summary Practice. Available from: https://health.ec.europa.eu/system/files/2021-10/glsp_en_0.pdf
4. EMA medical terms simplifier: Plain-language description of medical terms related to medicines use. April 2022. Available from: https://www.ema.europa.eu/en/documents/other/ema-medical-terms-simplifier_en.pdf
5. EMA. Draft Guidance document on how to approach the protection of personal data and commercially confidential information in documents uploaded and published in the Clinical Trial Information System (CTIS). Available from: https://www.ema.europa.eu/en/documents/other/draft-guidance-document-how-approach-protection-personal-data-commercially-confidential-information_en.pdf
6. EMA. Clinical Trials Regulation: progress on implementation. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation/clinical-trials-regulation-progress-implementation

EMWA News

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EMWA Ambassador Programme News

On Nov. 10, **Ricardo Milho** (EMWA Sponsorship Officer), **Sarah Choudhury** (EMWA Treasurer), and **Arunon Sivananthan** (EMWA member) (shown in the picture above) represented EMWA at the NetworkPharma Medcomms Career Event ("Working in and around #MedComms") that took place at the Radisson Hotel & Conference Centre in London Heathrow.

The event was well attended, with around 500 participants, including employers from Medcomms and Regulatory Writing agencies and newcomers with diverse backgrounds interested in starting a career in Medical Writing.

Sarah, Ricardo, and Arunon staffed an exhibitor table at the event and were extremely busy answering many questions about training for medical writers and the benefits of joining EMWA. They demonstrated the resources on the EMWA website and provided promotional information and copies of the EMWA journal *Medical Writing*.

Sarah also hosted a discussion panel in the afternoon entitled "Meet the Regulatory Writers", with 3 other writers from Regulatory Writing agencies who shared their career journeys and talked about what it is like to work in regulatory writing. Overall, it was a very successful day, and we look forward to further collaborations with **Peter Llewellyn** and NetworkPharma.

If you are an experienced medical writer and EMWA volunteer and are interested in becoming an EMWA Ambassador, or if you know of any upcoming career events in your locality, please contact Abe Shevack (aspscientist@gmail.com).

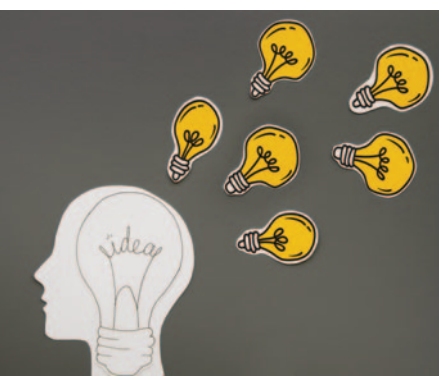
Recommendations for setting up a Special Interest Group (SIG)

EMWA Special Interest Groups (SIGs) are focus groups comprising EMWA members with a common interest who want to meet, discuss, and share information and best practices in their respective areas.

Such groups allow EMWA and its members to contribute to important conversations around topics that will impact medical writing in the future. EMWA SIGs are open to all EMWA members, and any EMWA member may propose and start a new SIG. The proposal to start a SIG should be sent via EMWA Head Office (info@emwa.org) to EMWA's Executive Committee for review and approval.

Please follow the recommendations for setting up a SIG described in this document: https://emwa.org/media/ 4629/sig-guide.pdf

Entrepreneurship Special Interest Group



The Entrepreneurship Special Interest Group (#EMWAEPSIG) intends to support EMWA members looking to expand their business.

The aim is to create a network of members who have taken the next step from working solo to running a company, whatever the business model. The intention is to create a professional space where members can access business advice and learn from the experiences of others at varying stages of their business development journey. Each member's contribution to the group's activities is valuable and unique. The EPSIG met on Thursday, December 1, 2022, to discuss the group's agenda for the next and future meetings. It was agreed to hold meetings on the last Wednesday of each quarter (1–2 pm UK time) in 2023.

Meeting dates:
Wednesday, March 29, 2023
Wednesday, June 28, 2023
Wednesday, September 27, 2023
Wednesday, December 20, 2023

EMWA Membership Hardship Fund

Would you like to remain or become an EMWA member again but cannot because of financial difficulties and challenging times? If so, EMWA would like to provide some assistance.

To be considered, you must be an existing or past EMWA member. There is no limit to the number of applications. With support from the EMWA Executive Committee (EC), the Treasurer will review each application and judge them on a case-by-case basis. We ask you to tell us a little about yourself through these questions:

- What are your career aspirations? (300-word limit)
- What are your plans for any future EMWA involvement? (300-word limit)
- Why do you need this fee waiver? (300-word limit)

In return, we ask you to make whatever monetary contribution you are able – and the rest EMWA will cover. If you cannot make any contribution at all, EMWA will not discriminate.

If you qualify, we will then review your case yearly. Hopefully, your situation will change; otherwise, we will consider supporting you through EMWA's hardship fund for a maximum of 3 consecutive years.

Details of anyone who qualifies will be kept strictly confidential by EMWA's Head Office.

This organisation's policy is to provide equal opportunities regardless of race, colour, religion, national origin, gender, sexual preference, age, or disability. EMWA, as a UN SDG partner organisation, aims to ensure inclusive and equitable quality education and promotes lifelong learning opportunities for all (UN SDG 4; https://sdgs.un.org/goals/goal4)

Please contact info@emwa.org and ec@emwa.org to apply.

EMWA volunteers

EMWA volunteers help to further the development of your association.

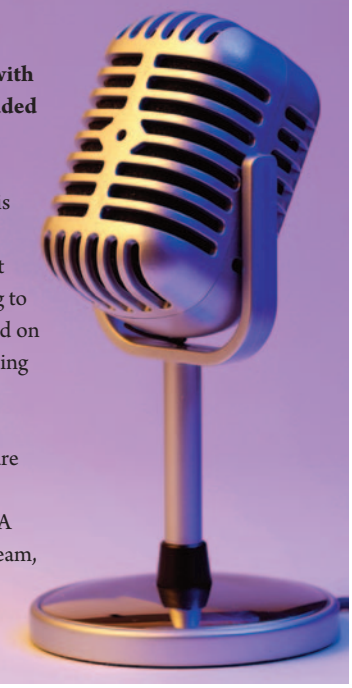
You can get involved in a very limited way or become part of a larger project. The choice is yours, and everyone shares in the benefits.

- Help promote the role of medical writers and strengthen our association.
- Help to raise the standards of your field.
- Increase your visibility and communication opportunities with other medical writing members.
- Add some prestige to your CV while participating in exciting activities.
- Improve your knowledge of medical writing and related topics.

If you are a member of EMWA and eager to support ongoing initiatives, please check the following page: https://www.emwa.org/about-us/emwa-volunteers/ Alternatively, contact the Public Relations officer (pr@emwa.org) to discuss other opportunities available.

EMWA Podcasts to be launched soon

EMWA will commence in 2023 with another outreach programme added to our menu – EMWA Podcasts.



The EMWA Podcasts programme is designed for a broad range of individuals, from those who are yet to begin a career in medical writing to those interested in staying informed on cutting-edge topics in medical writing or regulatory affairs.

With the goal of expanding the EMWA Podcasts programme, we are looking for volunteers to join the Podcasts team. If you are an EMWA member interested in joining the team, please email info@emwa.org.

Bringing decentralised clinical trial protocols to life

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Abstract

Decentralised clinical trials (DCT) use technology, processes, and services to reduce or eliminate the need for onsite visits. Use of DCT components within clinical trials is becoming widespread and protocols are pivoting from using DCT components as rescue tools during the COVID-19 pandemic to including them as integrated decentralised research methods. To date, there is no consolidated guidance for what DCT component content should be included in the protocol. To enhance clarity, completeness, and replicability in clinical trial protocols incorporating DCT components, this article outlines a simple scoping process for information gathering and summarises some common considerations around frequently used components. The objective of this article is to provide protocol authors with tools, resources, and guidance to better support the development of clinical trial protocols that include DCT components.

Introduction

Effective clinical trial protocols are clear, precise, practical, and consistent in communicating the trial purpose and activities to all stakeholders. Recent evidence has shown that protocol design is correlated with trial performance and protocol features can be relatively robust predictors of operational efficiency.[1,2] The more complex a protocol becomes, not only is the trial less likely to run well but there are also likely to be more amendments, longer trial times, and poorer recruitment and retention rates.[3,4]

There is a growing demand for adopting clinical trial approaches that reduce the burden on participants and increase recruitment and retention of a more equitable participant population.[5] Although decentralised clinical trials (DCTs) are not new (Pfizer's REMOTE trial started 12 years ago), it was during the COVID-19 pandemic that trial teams used DCT components as rescue tools to continue trial activities offsite when onsite visits were impractical. Given the nature of the public health emergency, regulatory agencies supported this approach; for example, the United Kingdom's Medicines & Healthcare products Regulatory Agency (MHRA) stated "It is entirely feasible and acceptable to prepare a protocol that incorporates appropriate descriptions of both the procedures for regulatory decision-making and flexibility in how clinical visits, monitoring of trial participants, follow-ups, etc. are implemented. Use of 'decentralised' and digital/virtual elements in a study should be considered".[6]

In the wake of the pandemic, research has shown that compared to traditional trial designs, trials using DCT components recovered faster from the impact of COVID-19.[7] Additionally, analysis has shown that DCT component use provides substantial cost savings and enhances participation.[8–11] This demonstrated trial resilience, combined with participant and economic benefit, will accelerate the transition of DCT components being used as pandemic "rescue tools" to integrated decentralised research methods. The protocol development process must be updated to enhance clarity, completeness, and replicability in clinical trial protocols incorporating DCT components.[12]

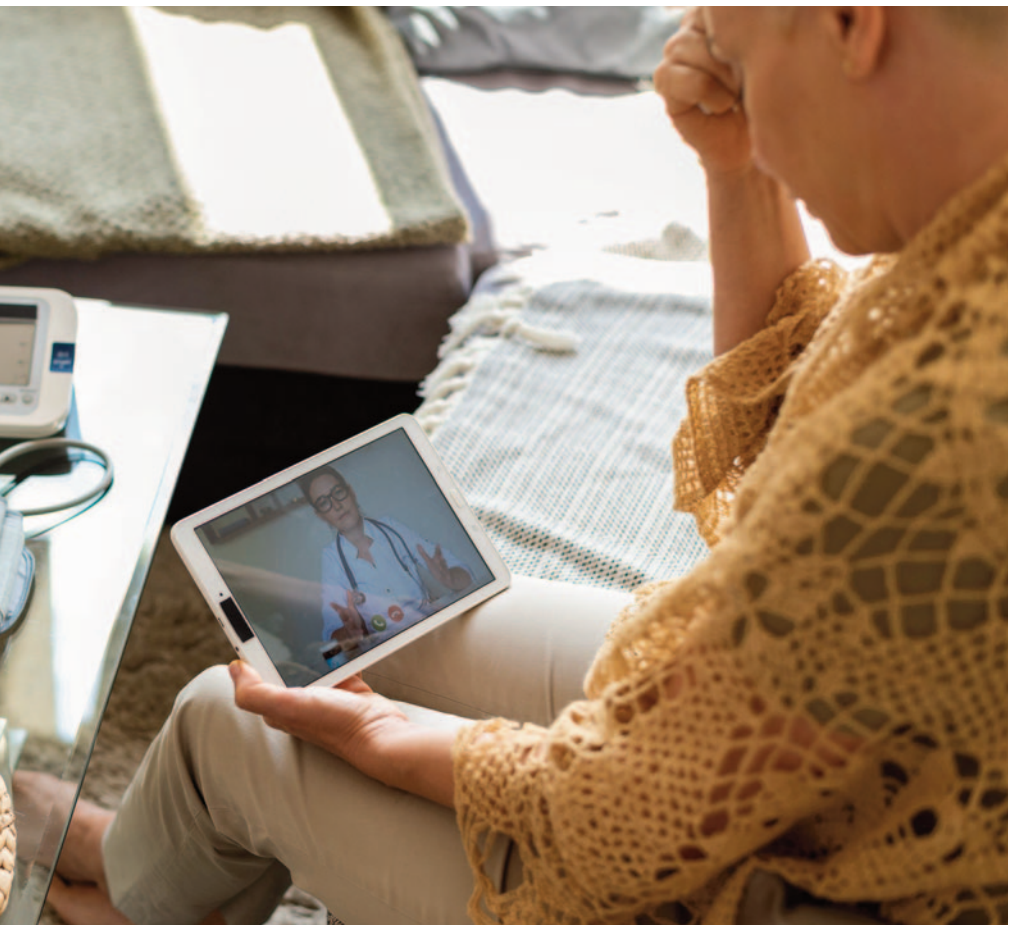
In this article, a simple scoping process is outlined alongside considerations for some frequently used DCT components. The objective of this is to provide protocol authors with tools, resources, and guidance to better support the development of clinical trial protocols incorporating DCT components.

This demonstrated trial resilience, combined with participant and economic benefit, will accelerate the transition of DCT components being used as pandemic "rescue tools" to integrated decentralised research methods.

What are decentralised clinical trials?

The most widely used definition of a DCT comes from the US FDA that defines a DCT as a trial in which some or all of the activities are conducted offsite. A more recent – and potentially more specific – definition comes from the Decentralized Trials & Research Alliance (DTRA) glossary that expands on the FDA definition to clarify that DCTs use technology, processes, and services to reduce or eliminate the need for onsite visits (Table 1).[13,14]

It should be noted that although certain activities or devices are considered to be DCT components, such as wearable or connected devices, a traditional trial with onsite visits does not automatically become a DCT just because it includes such a device – i.e. the DCT components need to materially reduce or eliminate the need to have onsite visits, not just provide an additional opportunity to collect data.



Subclassification of DCTs broadly separates DCTs into "full" or "hybrid" trials. Full DCTs are distinguished from hybrid trials by not requiring participants to go to trial sites at all – all trial-related activities are done at the participant's home or in another local setting.[15] By contrast, a hybrid DCT uses a blended form of onsite and offsite activities; thus, hybrid DCTs can cover a range of configurations.[14]

Scoping a DCT component

One of the most challenging aspects of protocol development is to understand the scope for each trial activity and how they relate and interact with each other – DCT components are no exception. The Association of Clinical Research Organization's (ACRO's) decentralised trials toolkit includes a map of common methods that can help visualise what is available and which methods work together.[16] Additional resources include the ACRO DCT Quality by Design (QbD) manual and the Digital Medicine Society (DiMe) playbooks for digital clinical measures and digital healthcare.[17,18]

These resources can aid discussion and further the trial team's understanding of the

Step	Scoping questions
Why	1. Why is the DCT component suitable for this research question? 2. Is the anticipated trial data quality appropriate for this study?
Who	1. Who is the DCT component's end user? 2. Who supports the data flow (point of collection to final storage)? 3. Who provides training?
What	1. What physical and/or digital items will be provided? 2. What data will be collected? 3. What training will be required?
Where	1. Where (what geographic regions) will the DCT component be used? 2. In what physical location (in relation to the end user) will the DCT component be used?
When	1. When will the DCT component be used in a given period (e.g., one day)? 2. How often in the given period will data be collected (e.g., discrete or continuous data)?
How	1. How will end users interact with the DCT component? 2. How will operational variability be controlled?

Figure 1. Scoping steps and key scoping questions for successful information gathering

prerequisites for DCT component use. Once understood, the DCT component information needs to be successfully incorporated into the protocol. The simple scoping exercise for each DCT component is shown in Figure 1; this approach is broadly aligned with the SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials) and the template for intervention description and replication (TIDieR) checklist and guide.[19,20] Although TIDieR is targeted towards enhancing the description of interventions in publications, the objective of improving reporting completeness and enhancing replicability is comparable to the objective here, so it serves as a suitable foundation to identify content required to adequately scope the DCT components.

It is important to note that the information collected as part of the scoping exercise may not be incorporated in the protocol in its entirety since there may be circumstances that would require some details to be omitted. For example, the name of a wearable or connected device may not be included if the trial is multiregional and local variability in the device is anticipated. In such circumstances, cross-referencing a supplementary document besides the protocol is preferrable.

Why?

The why is the first – and most important – point to address in establishing DCT component scope. A recent qualitative analysis has highlighted two key questions (this was reinforced in ACRO's recent Q&A resource).[12,21]

1. **Why is the DCT component suitable for this research question?**
   - Clear justification for why DCT components are being used in the trial.
2. **Is the anticipated trial data quality appropriate for this trial?** Consider:
   - Results generalisability (e.g. is a technologically literate population representative of the wider target population)
   - Participant preference (variability in data outcomes dependent on DCT component flexibility and participant familiarity with the component)
   - Big data (challenging datasets and unnecessary participant burden from continuous data collection)
   - Data completeness (missing data).

Both questions form the foundation for each DCT component's risk-benefit assessment. To aid this assessment, ACRO released a DCT risk assessment considerations template as part of their DCT toolkit.[17] This requirement is reinforced by the EMA's guideline on computerised systems and electronic data in clinical trials that states that the approach used to reduce risks (e.g., adoption of DCT components to reduce dropout risk) should be incorporated in the protocol design.[22]

> The *why* is the first and most important point in establishing DCT component scope: it consists of addressing the component's suitability for the research question and the appropriateness of the anticipated data quality.

Who?

The *who* in this context refers to the end user and any individuals supporting the end user, data flow, or training. For electronic devices or questionnaires, the end user is likely to be the participant but could also be a caregiver, family member, or other individual. By contrast, end users for home healthcare or electronic clinical outcome assessments are likely to be investigators, nurses, or other healthcare professionals. Regarding individuals supporting the end user, data flow, or training – summary details may be required to demonstrate that a robust process will be in place for the trial. For example, for a wearable or connected device with the participant as the end user, training may need to be provided by site staff during enrolment or by virtual means, and data flow from the device may be managed by the device vendor or the sponsor.

What?

What refers to what physical and/or digital items are provided, what data will be collected, and what training may be necessary. For example, physical items may include material and training documentation provided to the end user or supporting individuals, whereas digital items may include apps, data flow, and troubleshooting support processes. If the information is extensive or likely to differ across geographies, then cross-referencing a supplementary document besides the protocol may be preferrable.

Where?

Addressing the *where* involves answering two questions:

1. **Where (what geographic regions) will the DCT component be used?** For example, the trial may be multiregional or conducted in a single country where individual states may have a degree of autonomy (e.g. in the USA).
2. **In what physical location (in relation to the end user) will the DCT component be used?** For example, a participant may be using a wearable or connected device for their whole waking period whereas a nurse conducting home healthcare visits may be conducting them at the participant's home or another agreed location.

Regarding the first question: Over the last year or so, regulatory agencies have begun to release dedicated DCT guidance or guidance that addresses certain DCT components – including agencies in Denmark,[23] USA[13] India,[24] and Switzerland.[25] As the adoption of DCT components increases, it's likely countries will release or update guidance on what components can be used and under what conditions they can be used in a trial.

In relation to the second question, the physical location should be understood to describe the intended use and any risk mitigation strategies. For example, if home assessments are required once in the morning and once at night, then the risk mitigation may include setting up reminders and strategies if the participant is away from home for a prolonged period of time such as for work or for vacation.

When?

When relates to when and how often a DCT component will be used – i.e. what timeframe (such as number of times used in a day) and how frequently will the data be collected (such as all the time or occasionally). Data collection can be discrete, where it is collected at a single point of time (e.g. an assessment that is conducted once a day), or continuous, where it is collected continuously (e.g. a wearable or connected device that monitors heart rate for the entire time the participant is instructed to wear it).

How?

The *how* refers to how the end user will engage with the DCT component and how operational variability will be controlled. The trial team must

have a clear understanding of how end users are expected to engage with the DCT components under ideal settings and – to a limited degree – control variability in its real-world operation (e.g. what happens if someone doesn't complete a critical assessment upon awakening? Will they get a reminder?). The more critical the DCT component is to the trial (i.e. the *why*) the more important this consideration.

What makes a DCT component?

Categorisation of DCT components remains fluid and different organisations may classify components and approaches differently depending on business or logistic needs. Below are some of the most common categories; their definitions can be found in Table 1.

Telemedicine

Telemedicine in the context of a clinical trial refers to the use of telecommunication technology between investigators and participants to conduct remote clinical assessments (e.g. functional tests such as physical or neurological examinations, collection of clinical data such as participant assessment of intervention benefit, or discussion of remote data collection in conjunction with digital health technologies). Data collected from telemedicine visits often support key endpoints and as such, the more critical the data the more important the description in the protocol. Key points to consider are whether there is flexibility for onsite, telemedicine visits, or remote visits. In addition, the more critical the data the more likely risk mitigation strategies need to be described in the protocol, e.g. for telemedicine visits at critical time points, the site may use multiple reminders or additional phone calls to ensure scheduled telemedicine visits are not missed.

Applications (apps) and technology

Although no formal definition exists for participant apps and technology, communication and data transfer between participants and investigators or other trial staff may employ commercial or custom-made apps. These apps may be installed on a smartphone, tablet, or laptop for use with telemedicine visits, wearable or connected devices, electronic clinical outcome assessments (eCOAs), home healthcare, or other trial requirements. These electronic devices may be provided by the sponsor as a *provisioned device* for the duration of the trial or the apps may be installed on the participant's preferred device: *bring your own device* (BYOD) option.

The detail required in the protocol for apps and technology does not need to be substantial but sufficient to provide a clear understanding of what is being provided. For example, if the trial includes telemedicine visits, wearable or connected devices and eCOAs – will all data collection be performed through the same interface (e.g. smartphone app) or via several interfaces? Regarding technology, will provisioned devices or BYOD be required, or will this be per participant preference? If BYOD is preferred, what happens if an eligible participant does not have a compatible device? From a regulatory perspective, the risk-benefit for provisioned device versus BYOD is complex and requires careful consideration.[26,27]

Wearable or connected device

Wearable or connected devices include static or wearable devices that can support remote data collection directly from the participant (e.g. wearables like actigraphs that monitor activity levels) or their environment (e.g. air quality). Data collected can be stored locally or centrally and the process from point of collection to point of final storage is part of the *data flow*. According to the EMA's recent Q&A on GCP "a detailed diagram and description of the transmission of

Table 1. Definitions

Name	Definition	Source
Classification and subclassification		
DCT	A clinical investigation where some or all of the trial-related activities occur at a location separate from the investigator's location	FDA 2021
	A clinical trial utilising technology, processes, and/or services that create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site	DTRA Glossary of Industry Terms 2022
Full DCT	Trials executed through telemedicine, mobile/local HCPs and/or mobile technologies – and are thus not bound by the geographic limitations that affect traditional trials	Apostolaros et al 2020
Hybrid DCT	A suitably flexible scenario that partially eliminates the requirements for participants to visit a physical trial site to perform a protocol-required event that may have traditionally taken place onsite	DTRA Glossary of Industry Terms 2022
DCT Components		
Telemedicine	The use of electronic information and telecommunications technologies to support and promote long-distance clinical healthcare, patient and professional health-related education, public health, and health administration. Technologies include videoconferencing, the internet, store-and-forward imaging, streaming media, and terrestrial and wireless communications	DTRA Glossary of Industry Terms 2022
Applications and technology	Communication or data entry point or both between the site and participant that can be through a smartphone or tablet or laptop device provided by the Sponsor for the duration of the trial (provisioned device), or software can be installed on the participant's preferred device (BYOD)	None
Wearable or connected devices	Electronic devices that can be worn or carried on the body to allow personal data of the user to be monitored and measured through smart sensors that are embedded in the device	DTRA Glossary of Industry Terms 2022
eConsent	Electronic form that may include multimedia components such as images, audio, videos, diagrams, and a digital signature to aid the collection of the informed consent of a participant. Also, documents that the patient has been given the appropriate, and not coercive, written information to support their ability to give fully informed consent. Other examples of consent forms are assent forms.	DTRA Glossary of Industry Terms 2022
eCOA	Electronic capture of a measure that describes or reflects how a participant feels, functions, or survives during a clinical trial. Types of eCOAs include eClinRO measures, ePRO measures, eObsRO measures, and ePerfO measures	DTRA Glossary of Industry Terms 2022
Home healthcare	Home healthcare encompasses a wide range of healthcare services that are given to a patient in their home. A variety of providers may be involved, including but not limited to home health nurses, phlebotomists, doctors, among others. This care is typically provided during home health visits.	DTRA Glossary of Industry Terms 2022
Direct-to-patient shipping	Direct shipment of clinical supplies and investigational medicinal products to the participant's residence or other agreed upon location (e.g. participant's work)	DTRA Glossary of Industry Terms 2022

Abbreviations: BYOD, bring your own device; DCT, decentralised clinical trial; DTRA, Decentralized Trials & Research Alliance; eClinRO, electronic clinician-reported outcome; eCOA, electronic clinical outcome assessment; eConsent, electronic consent; eObsRO, electronic observer-reported outcome; ePerfO, electronic performance outcome; ePRO, electronic patient-reported outcome; HCP, healthcare provider.

electronic data should be provided in the protocol"; this recommendation is also supported by the ACRO QbD manual.[17,28] Additional points of caution include:

- Describing any flexibility related to how end users engage with the device to accommodate a range in technology capabilities and visibility or mobility
- Data collection and validation capabilities
- Handling missing or invalid data.[21,29,30]

Electronic Consent (eConsent)

eConsent is an electronic method for seeking, confirming, and documenting informed consent. DCTs that are fully remote are likely to require eConsent to be provided remotely via an app, whereas hybrid trials may require eConsent provision remotely or at the trial site. Although the consent process does not feature heavily in the protocol, the difference and variability in the eConsent process compared to the traditional paper consent does warrant careful evaluation during protocol development.

Electronic clinical outcome assessment (eCOA)

Much like conventional paper clinical outcome assessments (COAs), each eCOA will require summary details to be included in the protocol and consideration for how it will be accessed and by whom. For patient-reported outcomes (PROs), details for complete PRO reporting are described in the SPIRIT-PRO extension.[31] Additional complexities when describing eCOAs (including ePROs) is that they may be accessed from different apps by different end users – this will multiply the data flow considerations that are recommended to be included in the protocol.[17] Similarly, training requirements may be variable depending on the number of eCOAs and where the users are located, trained or both.

Home healthcare

Home healthcare by nurses, phlebotomists, physicians, or other healthcare professionals can relieve some of the trial participation burden by reducing or eliminating the need for onsite visits. The challenges in incorporating these into the protocol fall into two categories:

1. **Flexibility around who will be able to receive home healthcare.** For example, is home healthcare mandatory or optional in one or all geographies? Alternatively, can home healthcare be a flexible alternative to onsite visits per participant preference? Lastly, are all participants eligible for home healthcare? – e.g. will all participants in a subgroup that has more assessments be eligible for home healthcare?
2. **Flexibility around where *home* visits take place.** Although home healthcare is often considered to take place at the participant's home, logistically it may not always be feasible. For example, a participant may not feel comfortable with a healthcare provider in their home or may be spending a large part of their day or week away from their home. Other, prespecified safe locations or local clinics may be feasible alternatives.

Direct-to-patient shipping

Direct-to-patient shipping involves providing trial materials or trial interventions (or both) directly to the patient via some home delivery mechanism. Early engagement with clinical trial supply chain stakeholders is essential to allow the time needed to provide logistic and cost estimates as well as establishing the process for protecting personal data. Within the protocol, the preparation, handling, storage, and accountability of medication and samples needs to be clearly stated – as well as for who this applies to (e.g. there may be geographic restrictions on where this DCT component can be used).

Concluding remarks

As DCT component adoption becomes more popular and accepted in clinical trials, the protocol development process needs to keep pace if protocols are to maintain their effectiveness. The proposed scoping process and resources highlighted in this article may serve as tools and guidance to help protocol authors enhance clarity, completeness, and replicability in clinical trial protocols incorporating DCT components.

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The opinions expressed in this article are the author's own and not necessarily shared by his employer or EMWA.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. Smith Z, Bilke R, Pretorius S, Getz K. Protocol design variables highly correlated with, and predictive of, clinical trial performance. Ther Innov Regul Sci. 2022 Mar;56(2):333–45 doi:10.1007/s43441-021-00370-0
2. Wu K, Wu E, DAndrea M, et al. Machine learning prediction of clinical trial operational efficiency. AAPS J. 2022;24(3):57. doi:10.1208/s12248-022-00703-3
3. Schueler, P. Innovation in clinical trial methodologies: Lessons learned during the Corona pandemic. 1st ed. Academic Press; 2020.
4. Forjanic Klapproth, J. Reaping the benefits from improved clinical trial protocols. H1 Virtual Events. June 2021 [cited 2022 Nov 11]. Available from: https://dev.trilogywriting.com/wp-content/uploads/2021/09/REAPIN1.pdf
5. US FDA. Advancing oncology decentralized trials – modernizing evidence generation. July 27, 2022 [cited 2022 Nov 9] Available from: https://www.fda.gov/about-fda/oncology-center-excellence/ advancing-oncology-decentralized-trials
6. Medicines and Healthcare products Regulatory Agency. Guidance on minimising disruptions to the conduct and integrity of clinical trials of medicines during COVID-19. Nov 13, 2020 [cited 2022 Nov 09.] Available from: https://www.gov.uk/guidance/guidance-on-minimising-disruptions-to-the-conduct-and-integrity-of-clinical-trials-of-medicines-during-covid-19
7. Price J, Goodson N, Warren EJ, et al. Resilient design: Decentralized trials recovered faster from the impact of COVID-19 than traditional site-based designs. Expert Rev Med Devices. 2021;18(sup1):1–4.
8. DiMasi JA, Smith Z, Oakley-Girvan I, et al. Assessing the financial value of decentralized clinical trials. Ther Innov Regul Sci. 2022 Sep 14:1–11.
9. de Las Heras B, Daehnke A, Saini KS, et al. Role of decentralized clinical trials in cancer drug development: Results from a survey of oncologists and patients. Digit Health. 2022 May 25;8:20552076221099997 doi:10.1177/20552076221099997

10. Haynes RM, Sirintrapun SJ, Gao J, McKenzie AJ. Using technology to enhance cancer clinical trial participation. Am Soc Clin Oncol Educ Book. 2022 Apr;42:1-7.
11. Adams DV, Long S, Fleury ME. Association of remote technology use and other decentralization tools with patient likelihood to enroll in cancer clinical trials. JAMA Netw Open. 2022 Jul 1;5(7):e2220053.
12. Association of Clinical Research Organizations (ACRO) Decentralized clinical trials: the change management Q&A resource [cited 2022 Nov 9] . Available from: https://www.acrohealth.org/dctqanda/
13. US FDA. Digital health: technologies for remote data acquisition in clinical investigations, draft guidance. December 2021 [cited 2022 Nov 9]. Availble from: https://www.fda.gov/media/155022/download
14. Decentralized Trials & Research Alliance (DTRA). Glossary of Industry Terms and Definitions [cited 2022 Nov 9]. Available from: https://www.dtra.org/1a-glossary
15. Apostolaros M, Babaian D, Corneli A, et al. Legal, regulatory, and practical issues to consider when adopting decentralized clinical trials: Recommendations from the clinical trials transformation initiative. Ther Innov Regul Sci. 2020;54(4):779–87.
16. Association of Clinical Research Organizations (ACRO). ACRO's decentralized trials toolkit [cited 2022 Nov 9]. Available from: https://www.acrohealth.org/dctoolkit/
17. Association of Clinical Research Organizations (ACRO). ACRO's quality by-design manual for decentralized trials and template for risk assessment considerations [cited 2022 Nov 9]. Available from: https://www.acrohealth.org/dctqbdmanual/
18. Digital Medicine Society (DiMe) The Playbooks: Better health powered by digital medicine [cited 2022 Nov 9]. Available from: https://www.dimesociety.org/tours-of-duty/the-playbooks/
19. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
20. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.
21. Coyle J, Rogers A, Copland R, et al.; of the Trials@Home Consortium. Learning from remote decentralised clinical trial experiences: A qualitative analysis of interviews with trial personnel, patient representatives and other stakeholders. Br J Clin Pharmacol. 2022 Mar;88(3):1031-42.
22. EMA Guideline on computerised systems and electronic data in clinical trials. Draft version. June 10, 2021 [cited 2022 Nov 9]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf
23. Laegemiddelstyrelsen Danish Medicines Agency. The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products. Version 2.0, September 2021 [cited 2022 Nov 9]. Available from: https://laegemiddelstyrelsen.dk/en/news/2021/guidance-on-the-implementation-of-decentralised-elements-in-clinical-trials-with-medicinal-products-is-now-available/~/media/5A96356760ED408CBFA9F85784543B53.ashx
24. Indian Society for Clinical Research (ISCR). DCT position paper: Decentralized clinical trials (dct) – a landscape assessment with recommenda-tions for growing the ecosystem by indian society for clinical research (ISCR) 2022. March 4, 2022 [cited 2022 Nov 9]. Available from: https://www.iscr.org/files/Article/1317861265_ISCR-DCT-Position-Paper-[Fina.pdf
25. Swissmedic and Swissethics: Position paper on decentralised clinical trials (DCTs) with medicinal products in Switzerland. Version 2.0, December 15, 2022 [cited 2023 Jan 13]. Available from: https://www.swissmedic.ch/dam/swissmedic/de/dokumente/bewilligungen/klv/positionspapier-dct.pdf.download.pdf/DCT_EN_.pdf
26. Mowlem FD, Tenaerts P, Gwaltney C, Oakley-Girvan I. Regulatory acceptance of patient-reported outcome (pro) data from bring-your-own-device (BYOD) solutions to support medical product labeling claims: Let's share the success stories to move the industry forward. Ther Innov Regul Sci. 2022;56(4):531–5.
27. Demanuele C, Lokker C, Jhaveri K, et al. Considerations for conducting "bring your own device" (BYOD) clinical studies. Digit Biomark. 2022;6(2):47–60.
28. EMA Q&A: Good clinical practice (GCP) [cited 2022 Nov 9]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/ qa-good-clinical-practice-gcp
29. Huh KY, Jeong SI, Yoo H, et al. Lessons from a multicenter clinical trial with an approved wearable electrocardiogram: Issues and practical considerations. Transl Clin Pharmacol. 2022;30(2):87–98.
30. Day JO, Smith S, Noyce AJ, et al. Challenges of incorporating digital health technology outcomes in a clinical trial: Experiences from PD STAT. J Parkinsons Dis. 2022;12(5):1605–9.
31. Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO Extension. JAMA. 2018;319(5):483–94.

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Pens for Kids

A pen is something that you would expect every medical writer to have on their desk – or close by in a drawer at least! Most likely you have a collection of pens from different companies, congresses, trade fairs and so on scattered around your house. But what about the children who do not possess one? How can they continue with their education?

Pens for Kids began in Denmark as a not-for-profit organisation focused on sending pens and pencils to children around the world who cannot afford such items for their education.

The work of Claus Hjørnet and his wife Mette has inspired the founding of some sister organisations – including Pens for Kids Switzerland (www.pens-for-kids.com), which was began by ex-EMWA Executive Committee member Diarmuid De Faoite, his wife Martina and their friend Jörg. Since it started in late 2020, thousands of pens and pencils have shipped from Switzerland to children in need in Tanzania, Kenya and Uganda.

Their work has been supported by the EMWA Sustainability Special Interest Group (SUS-SIG). If you are coming to the Prague conference, you can finally declutter your desk by donating any working, but no longer needed, pens or pencils to the donation box that will be placed in the venue.

A final word of thanks goes out to EMWA members Heather Mason and Raquel Billiones who have been strong supporters of Pens for Kids.

How can you help?

1. Bring your no-longer-needed pens and pencils to the Prague conference. We will have a pen collection box for you.
2. Donate pens or money towards shipping through www.pens-for-kids.com
3. Check if there is a local Pens for Kids branch near you

- UK: www.pensforkids.co.uk
- Denmark: www.pensforkids.dk
- Switzerland: www.pensforkids.ch (German language site)

Peer review of a clinical trial protocol: Practical tips for regulatory medical writers, clinicians, and clinical scientists

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Abstract

Protocol development is a critical milestone in the clinical drug development process for all pharmaceutical companies conducting clinical trials. A regulatory medical writer (RMW) plays a crucial role in the protocol development and peer review processes along with different stakeholders. Poor peer review leads to protocol amendments, which delay regulatory submission and increase project costs. Thus, there is a strong need for RMWs and stakeholders to work together during the peer review process to highlight the specific issues that should be addressed before finalisation, which helps in creating effective, efficient, and high-quality protocols. The suggested protocol peer review steps described in this article will help an RMW to plan, coordinate, and deliver this highly important document for global and local clinical trials.

Introduction

Clinical trial protocol development and peer review processes are vital to the clinical development programme of pharmaceutical companies and contract research organisations (CROs). These processes result in the successful submission of a systematically reviewed clinical trial protocol to regulatory authorities for their expert opinions and approval.[1] The clinical trial protocol peer-review process is where many "experts" examine the proposed trial to consider aspects such as study design, trial procedures, subject eligibility, feasibility, acceptability, and study endpoints.[2, 3, 4] A review of the clinical trial protocol by scientific experts is crucial for a regulatory medical writer (RMW) to generate a high-quality protocol for regulatory submission.[5] Hence, an RMW needs a comprehensive understanding of the peer-review process and steps[6] that must be followed during the peer review of a clinical trial protocol and other clinical regulatory documents. Therefore, we have made an effort to provide practical advice to an RMW regarding the peer review process of the clinical trial protocol to enhance the value and efficiency of the protocol review process. This process will help to avoid poor review practices in pharmaceutical companies, CROs, and knowledge process outsourcing (KPO).

Peer review process

Peer review is a process in which subject matter experts review each other's work to meet the accepted high standards of their discipline and disseminate research data to ensure that unwarranted claims, unacceptable interpretations, or personal views are not presented without prior expert review.[2]

The peer-review process can be inefficient and challenging for writers and peer reviewers when there is a communication gap between the two. Thus, effective coordination between peer reviewers (stakeholders) and RMWs is essential to ensure that the peer-review process runs efficiently. The peer-review team (Figure 1) and the peer-review process (Figure 2) add substantial value to the clinical protocol development (Figure 3). In this process, stakeholders are responsible for the design, scientific aspects, regulatory, ethical and legal requirements of the protocol, and RMWs are accountable for ensuring the consistency, accuracy, formatting, and finalisation of the protocol.[3, 7, 8]

We list below steps for RMWs to encourage efficient review of the protocol within the pharmaceutical industry, CROs, and KPO. It is also recommended that all stakeholders follow these tips for an efficient review.

Peer reviewers in a clinical protocol development

Different stakeholders play a vital role during the peer review of the clinical protocol. The various stakeholders and their expertise for the protocol review are presented in Table 1.[1, 7, 9, 10, 11]

The peer review team composition can vary depending on the type of study and study design (Figure 1).

The peer reviewers should consider the crucial elements for an effective peer review, which will help develop a high-quality protocol (Table 2).

Kick-off meeting

The RMWs and stakeholders must collaborate effectively during the peer review process. The best way to collaborate and communicate during the peer review process is to set up a kick-off meeting[1,12] with all the stakeholders to understand the roles and responsibilities of the team members, training needs, data sources for review, instructions and expectations about the review, maintaining meeting minutes and action items, the review cycles, the timelines, and comments resolution process. When developing a global clinical trial protocol, the stakeholders may be located in different locations; hence the kick-off meeting is usually organised virtually. An RMW should know the time differences in different countries to achieve a robust peer-review process. An RMW must consider the following steps before, during, and after a kick-off meeting:

When developing a global clinical trial protocol, the stakeholders may be located in different locations; hence the kick-off meeting is usually organised virtually.

Before meeting:

- Consider the various time zones where the team members are located. Confirm a virtual meeting time with different stakeholders through e-mail before sending any meeting invitation.
- Ensure that each particular protocol section's responsible subject matter experts are identified and invited to the meeting.
- Ensure that all invitees have access to the virtual meeting platform.
- Have all the virtual meeting details (time, link, participants' details, agenda, protocol

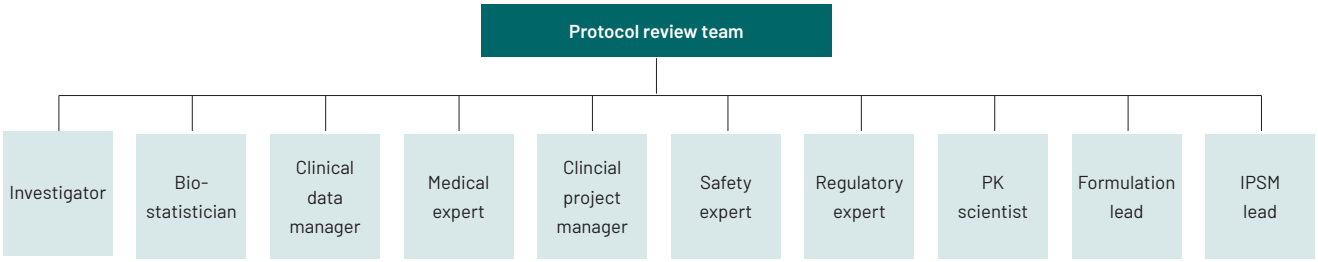

Figure 1. Recommended clinical protocol peer review team composition

Abbreviations: PK, pharmacokinetic; IPSM, investigational product supply management

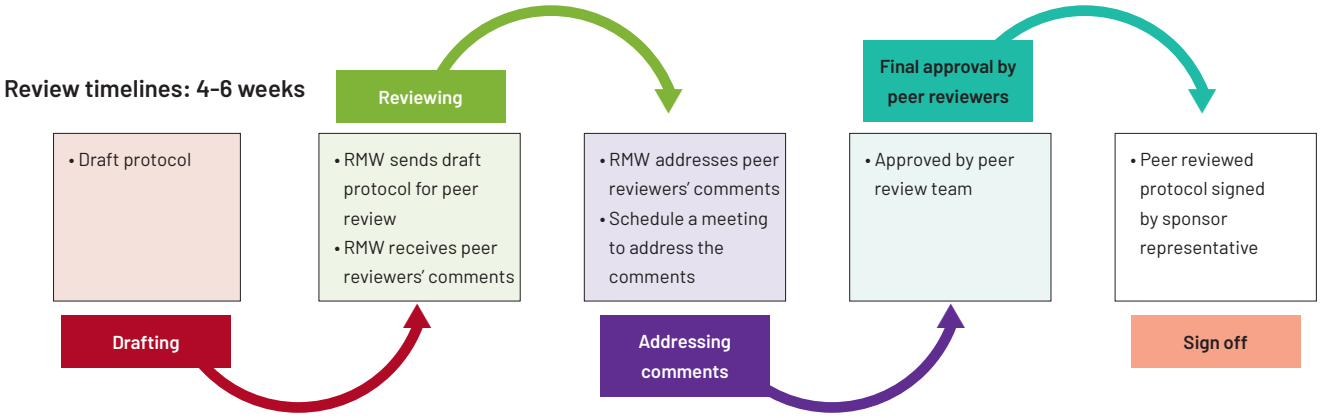

Figure 2. Recommended clinical protocol peer review process flow

Abbreviation: RMW, regulatory medical writer

Table 1. Stakeholders and their opinions on protocol review

Peer review team composition and their opinions on key elements	Peer review team composition and their opinions on key elements
1 Investigator • Feasibility of a trial • Trained and experienced resources • Significant risks in a trial • Inclusion and exclusion criteria of patients • Operational challenges • Benefit and risk ratio in the current trial	**5 Clinical project manager** • Description of study conduct • Feasibility of a trial • Optimal execution of a study • Operational challenges
2 Medical expert • Study design • Inclusion and exclusion criteria • Primary and secondary objectives • Endpoints • Assessment procedures • Use of concomitant therapies or the stopping rules to be applied in the study • Scientific expert on regulatory queries and their responses • Operational challenges	**6 Safety expert** • Description of the drug surveillance program, including medical reviews for safety reporting, safety databases, necessary follow-up, risk assessment, and products relatedness
3 Biostatistician • Statistical procedures, methods, and interpretation of endpoints • Safeguards the minimisation of potential variability in the study • Precautions to prevent various forms of bias in the protocol	**7 Regulatory expert** • Ensure compliance with the FDA and international regulations/ interpretations/guidelines for designing and conducting a clinical trial protocol
4 Data manager • Key data items to be collected and the frequency of collection with respect to the visit schedule for the development of paper Case Report Form (CRF) or eCRF • Ensure that data elements are complete and reliable • Identify any missing key data elements in a protocol	**8 Pharmacokinetic (PK) scientist** • Description of PK objectives and endpoints, dosing procedures and dosing frequencies, PK requirements, and statistical procedures for evaluating PK data
	9 Formulation lead • Ensure adequate preparation and form of a drug, which is both stable and acceptable to the patient throughout the study
	10 Investigational product (IP) supply management lead • Description of good manufacturing practices for preparing, storing, packaging, labeling, and distributing the IPs to the study sites

synopsis/outline/concept sheet, and other source documents) ready one day before the meeting. Check the technical functions of the virtual meeting technologies beforehand to avoid technical glitches during a meeting.
- Confirm the contact details and availability of the attendees.
- Prepare a checklist before initiating any kick-off meeting to facilitate a productive discussion.

During meeting:
- Ensure having a stable internet connection and clear audio during the virtual meeting. Important information can be missed in case of audio issues.
- Remember to mute yourself if you are not speaking.
- Listen carefully to the discussion and take notes for future reference.

After meeting:
- Prepare the meeting minutes and distribute them to help all stakeholders for the next meetings. The meeting minutes will help the team with further actions and planning.

Tools and techniques for peer review

Version control

The version control of the clinical protocol is a crucial step in the peer review process. In many cases, an RMW receives multiple versions/texts from different stakeholders as e-mail attachments/e-mail texts.[6] This poses challenges to keeping track of various versions, consolidating comments, and reconciling issues in the next draft of the protocol. The RMW can potentially miss essential comments from the critical reviewers, leading to poor protocol quality. Thus, the review team should use common document management tools as an effective method to maintain the versions of the protocol during the peer review process.

Document management systems

As per Good Clinical Practice (GCP), the sponsor should validate all the computerised systems based on a risk assessment that considers the system's intended use and the system's potential to affect human subject protection and the reliability of trial results. Hence, GCP-compliant systems are essential in the peer review process. A lot of electronic tools[6] are available to perform the peer review of the protocol/other

Figure 3. Significance of peer review in cinical protocol development

documents, which will help to achieve effective review and version control of the protocol. Below is a non-exhaustive list of potential tools.

- Veeva Vault
- PleaseReview
- Citrix Software
- Shared Network Directory
- Lotus Notes
- Documentum/Document Management Software

The above document management systems support the serial review process where all the reviewers can review the documents simultaneously and see comments from other team members. These document management systems show who checked out the document, when and when it was checked back in and keep track of versions and updates in the document management system. It is essential that a system available and familiar to all stakeholders is used.

Comments resolution and conflict management

The clinical trial protocol development is crucial in running a critical trial. An RMW should be well-versed in international requirements, regulatory guidelines, templates, and style guides. It is essential to provide training materials, standard operating procedures (SOPs) (sponsor's SOPs and CRO's SOPs), work instructions, and other guidance documents necessary for protocol development.

An RMW should consider the following recommended techniques to manage the demanding situations for the peer review process of the protocol.

Structured comments/review technique

An RMW should clarify what they want the reviewers to focus on and how comments should be added to the protocol during the kick-off meeting for a focused and effective review. Generally, a strategic review is needed to focus on the data's content and scientific validity. It should not focus on inconsistencies, numbers, spelling errors, abbreviations, language, editorial, style, citations, cross-references, and overall formatting.

Early delivery technique for the review

There may be situations wherein the peer review of the protocol was delayed due to the complex

Table 2. Crucial elements to consider during peer review of a protocol [7, 8]

Section	Crucial elements for peer review
Introduction	a. Current prevalence and incidence of disease b. The rationale for the choice of study design elements c. The goals for doing this particular study at this point d. Description of research question and justification for undertaking the trial, including a summary of relevant studies e. An unmet medical need for any indication f. Known and potential risks and benefits g. An explanation for the choice of comparators h. Drug and disease-specific background information, including the safety information available i. Competing products on the market
Objectives	a. Should present the question(s) that the study is designed to answer b. Verify clearly whether the trial is planned for superiority, noninferiority, exploratory, and scientific rationale for these
Evaluations and endpoints	a. Evaluate the necessity to conduct this trial at this stage b. Evaluate the necessity to combine this trial with another trial, if applicable c. Do the endpoints support the objectives of the study? d. Are the endpoints clinically and scientifically valid for the disease being studied? e. Are the estimands clearly indicated? f. Are the endpoints chosen the best ones to measure? g. Verify the tools, instruments/questionnaires, and laboratory tests that will be used to gather the data for the efficacy endpoints h. Review evaluations required for both primary and secondary endpoints i. Review the references for the development and validation of instrument content j. Verify the patient population in which the questionnaire was validated, with special attention to the current study population k. Verify the specific time points and their acceptability to the regulatory authority (e.g., change from baseline to Week X). Consider including the definitions of the derivation, use, and timing of a composite endpoint
Hypothesis	a. Types of hypotheses used in the trial and reasons for the selection b. Verify whether any hypothesis is stated in the protocol. If not, a convincing reason not to state a hypothesis should be verified in the protocol c. Statements of hypotheses should consider the endpoints being studied, including the time at which the endpoints are measured, such as the day or week or specific visit d. The hypothesis should not be a rewording of the objectives. Verification of the study hypothesis is a very important aspect of the study. Review this carefully.
Study design	a. Is the design itself the best one for this trial? Why? Have the authors considered other designs? b. Can the chosen design control major sources of bias? c. What is being done to minimise the placebo response? d. Feasibility for patients and doctors e. Does it have to be randomised? If so, why? f. Method of assigning treatment to subjects (e.g., randomisation) or other measures to be taken to minimise bias, including key stratification variables g. Level of blinding (e.g., open-label, double-blind) h. Competition for this trial, for the patient population, for institutions, and for industry trials i. If a specific study setting is required, please describe (e.g. community clinic, tertiary care hospital) j. Explanation of sequence and duration of study phases/periods, including any follow-up phase, and expected duration of subject participation k. Review the end of study definition l. Choice of control: If an active control is used, indicate whether the intent is to establish superiority, noninferiority, or equivalence of the study drug under investigation compared with the active control m. The rationale for choosing the study population, level of blinding, treatment groups, dosage and dose administration interval, route of administration, treatment period, control selection, efficacy measures, length of study phases and periods

Section	Crucial elements for peer review
Time and events schedule	a. Review the efficacy and safety parameters, pharmacokinetic, pharmacodynamic, biomarker, pharmacogenomic, immunogenicity, or other measurements and their frequency/timing, regarding the time and events schedule b. Can any procedures be eliminated or reduced in number/frequency? c. Can any patient visits be eliminated? d. Can any tests conducted at any visit be eliminated? e. Does the protocol list what is to be done at each visit? f. Do the patient visits and assessments match those presented in the Table of assessments?
Eligibility criteria	a. Are they necessary for the trial? b. Is this reasonable? Are they too restrictive? If so, can they be relaxed? Not restrictive enough? c. What about other health problems (for example, diabetes)? Could some be eligible? d. Life expectancy criterion – what is it based on? Is this necessary? e. Are there any inclusion criteria that can be eliminated? f. Are the inclusion criteria going to create the most appropriate group of patients regarding the ability to extrapolate the data? g. Are the inclusion criteria realistic in terms of patient recruitment?
Patient population	a. Is the population to be studied the most relevant one to meet the company's goals? b. Does the study population have appropriate gender and minority representation? c. Does the study population contain elderly patients? (Should it?)
Blinding (if applicable)	a. Is this issue adequately addressed? b. Are all groups blinded that should be blind (i.e. those who interact with the primary investigator, patients, staff at the site, and sponsor)? c. Does the protocol adequately deal with the question of blinding the drug container, packaging labels and how to unblind patients in cases of problems?
Concomitant therapy	a. Does the protocol deal appropriately and adequately with this issue? b. Does the protocol list acceptable and unacceptable prescription drug therapy, over-the-counter drugs, and other nonprescription products and the terms under which each may be used?
Patient compliance	a. Is patient compliance being monitored or measured in this trial? If so, how? b. Is this the best way, and have other ways been considered?
Safety reporting	a. Ensure the compliance of country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards /independent ethics committees, and investigators
Pregnancy reporting	a. Ensure the compliance of collection of pregnancy information and reporting of pregnancy, including abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
Contraception guidelines	a. Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies
Data protection	a. Is the data protection section included in the study protocol? b. Ensure compliance with the applicable rules on the protection of personal data and any relevant information on measures to be taken in case of a data security breach
Start and end of study	a. Is the clear end-of-study definition included in the study protocol? b. Is the clear study completion definition included in the study protocol? c. Verify if there is any difference in the end-of-study definition and study completion definition as per regulatory requirements
Stopping criteria	a. Verify a description of the stopping rules or discontinuation criteria for individual subjects, study periods of the clinical trial, and the entire clinical trial
Compliance with ethical and regulatory requirements	a. Is the study protocol designed and developed in compliance with applicable ethical and regulatory requirements? b. If applicable, does the study protocol follow specific guidance documents for specific indications or therapeutic areas?

work environment and conflicting resources with projects. Delays can lead to poor protocol review due to insufficient review time. Thus, an RMW should coordinate with all the stakeholders and target to complete the peer review process before the delivery date (2 to 3 days before the review timeline). This will enable the completion of the protocol on time.

Comments management techniques[1,13]

Too many reviewers can lead to conflicts and contradictions. An RMW can propose to minimise the number of reviewers (one subject matter expert per function) during the peer review. If there are multiple reviewers per function, an RMW can request a consolidated set of comments per function, with one contact person coordinating per function.

The best way to resolve comments is to set up a comments resolution meeting[1] with all the stakeholders. Differences of opinion should be discussed openly till a consensus is reached.

Too many reviewers can lead to conflicts and contradictions. An RMW can propose to minimise the number of reviewers (one subject matter expert per function) during the peer review.

Crucial instructions/ expectations technique for review

In many cases, the peer review process expectations are unclear to reviewers. Thus, an RMW should clarify the following expectations for the peer review of the protocol during their first meeting with the reviewers:

- Reviewers' responsibilities, review process, and timelines
- Familiarity with the current SOPs and current regulatory guidelines
- Familiarity with the data sources (protocol synopsis/concept sheet/outline, the current version of the investigator's brochure, product label, a summary of product characteristics, and recent literature, if applicable)
- Instructions for electronic tools
- Familiarity with the document type and document development stage
- Expectations for categorisation of review comments
- Expectations for strategic input on content in the form of specific, actionable, and relevant comments
- Back-up plan for review
- Training requirement, if any

Training the reviewers[1,6,12]

All the team members who are involved in reviewing a protocol should receive compulsory training for the following:

- How to review documents
- How to give comments (content-related, actionable, not editorial or stylistic)
- How to prioritise comments (critical, major, and minor)
- How to respond to other reviewers' comments
- How reviewers should focus primarily on their area of expertise
- Training on electronic tools (confirm access, the familiarity of a tool, and difficulties)
- Any other training for new reviewers

Benefits of comprehensive peer review of a clinical protocol

Scientific support and benefits to the regulatory medical writer

All the peer reviewers are experts who provide scientific comments to the RMW. The success of peer review depends on each reviewer focusing on their area of expertise and trusting their teammates to focus on theirs. Peer reviewers should make changes in track change mode along with comment boxes that would be more helpful and efficient for a writer.

Scientific and technical support to different stakeholders

An RMW should be well versed with guidance documents, technical tools, medical and therapeutic area knowledge, language and grammar, regulatory, ethical and legal requirements, and formatting/editing tools. All the above skill sets and experiences are crucial in developing a good protocol, which will help all the stakeholders to achieve a significant milestone in the clinical development programme.

Support the regulatory team to achieve submission on time

A thoroughly reviewed protocol can avoid any significant protocol amendments, which will speed up the regulatory submission and save the project costs.

Summary

In summary, regulatory submission of a clinical trial protocol is a significant milestone for pharmaceutical, CROs, and other stakeholders in the healthcare industry. The demand for an

expert RMW who can accelerate such regulatory submissions with high-quality documents is increasing day by day across the globe. RMWs are an essential part of the protocol preparation and review team. The protocol peer review steps will help an RMW plan, initiate, coordinate, and complete the peer review process. Protocol development team members/stakeholders benefit from an RMW who understands the protocol development and peer-review process, stakeholder's roles and responsibilities, document management systems, and project timelines, which will help produce a high-quality document.

Conflicts of interest and disclaimers

The authors declare no conflict of interest. The opinions expressed here are solely those of the authors and not necessarily those of Sun Pharma Advanced Research Company Ltd.

References

1. Radovan D. Help reviewers tell you what they want. Med Writ. 2018;27:4.
2. Kelly J, Sadeghieh T, Adeli K. Peer review in scientific publications: Benefits, critiques, & a survival guide. EJIFCC. 2014;25(3):227.
3. Sharma S. How to become a competent medical writer? Perspect Clin Res. 2010;1(1):33.
4. National Institute for Health and Care Research. Clinical trials toolkit. Available from: https://www.ct-toolkit.ac.uk/routemap/peer-review/
5. Sharma S. Development of medical writing in India: Past, present and future. Perspect Clin Res. 2017;8(1):45.
6. Bernhardt SA. Improving document review practices in pharmaceutical companies. J Bus Tech Commun. 2003;17(4):439–73. doi:10.1177/1050651903255345
7. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346. doi:10.1136/bmj.e7586
8. Integrated addendum to ICH E6 (R1): Guideline for good clinical practice E6 (R2). Current Step 4 version dated. 2016.
9. Adams-Huet B, Ahn C. Bridging clinical investigators and statisticians: Writing the statistical methodology for a research proposal. J Investig Med. 2009;57(8):818–24. doi:10.2310/JIM.0b013e3181c2996c
10. Krishnankutty B, Bellary S, Kumar NB, Moodahadu LS. Data management in clinical research: an overview. Indian J Pharmacol. 2012;44(2):168.
11. Moro-Martin L. Writing a clinical trial protocol: Expert tips March 23, 2020. Available from: https://www.kolabtree.com/blog/how-to-write-a-clinical-trial-protocol/.
12. Fiebig D. Back to the future or the amazing lack of progress in effective document review. Med Writ. 2015;24:3.
13. Cuppan GP, Bernhart SA. Missed opportunities in the review and revision of clinical study reports. J Bus Tech Commun. 2012;26(2):131–70. doi:10.1177/1050651911430624

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Transition to the EU Clinical Trials Regulation: Trick or treat?

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Abstract

The etiquette in clinical trial research requires companies to respect rules and to be precise and accurate. The new EU Clinical Trials Regulation 536/2014 (EU CTR) pushes companies and health authorities one step further – to be more flexible and collaborative. The EU CTR aims to harmonise clinical trial applications in the EU, bring more innovation to Europe, and enable faster approval of clinical trials. However, the novel process of clinical trial application in its early stages is fraught with technical and logistic challenges.

Introduction

Every new year brings new changes, not only in our personal lives but also in the regulatory landscape. 2021 was the final year of the transition of Medical Devices Directives (Directive 93/42/EEC and Directive 90/385/EEC) to the Medical Devices Regulation (EU) 2017/745.[1] The hottest topic in 2022 was the transition of the Clinical Trial Directive to the Clinical Trials Regulation 536/2014 (EU CTR). The aim of the regulation is to improve the transparency of conducting clinical trials, support innovative clinical trials, and simplify and harmonise the rules (see Table 1).[2]

The regulation was adopted in 2014 and the implementation was planned in December 2015. Due to various technical reasons (technical difficulties, strategical changes, and the audit of the novel system), the submission platform was officially released in January 2022.[3] As of January 31, 2023, the Clinical Trial Directive has been completely superseded by the EU CTR.[2,4] The transitional period for ongoing clinical trials that are performed under the Directive is still ongoing until 2025 (except for the non-interventional studies).

Clinical trial application then and now

THEN: Prior to January 31, 2023, a clinical trial application (CTA) submission had to be done nationally.[4] This meant that a sponsor who wants to conduct a multinational trial in 20 countries in the European Union/European Economic Area (EU/EEA) had to submit 20 national CTAs and adapt the documentation according to the different national legislations.

NOW: Under the EU CTR, all clinical trials that have been submitted nationally in the EU/EEA (except the non-interventional studies) by January 31, 2023, must be transitioned and uploaded to the new Clinical Trials Information System (CTIS) by 2025.[5] The major change is the centralised submission of clinical trial applications (CTA) in the EU through the CTIS portal. The assessments by competent authority and ethics committee can be done in parallel, and the validation/assessment questions are communicated via Request for Information (RFI) by the Member States.

Furthermore, the regulation introduced a so-called winter clock stop – a period from Decem-

Table 1. Pros and cons of the Clinical Trials Regulation

Pros	Cons
Single submission for the EU countries and to the ethics committee as well as competent authorities at the same time	New system – new challenges
Document consistency in all Member States (MSC)	Complicated procedure for smaller and less innovative clinical trials?
Channelling questions through one country – RMS (Reporting Member State)	Single substantial modification submission per clinical trial, the next submission of a substantial modification is only possible if the first procedure has been approved
Defined timelines – faster approval	Tight timelines in general
Lower documentation burden for multinational clinical trials	Other Member States (MSC) can still contact the sponsor and request documentation
Harmonisation of the rules for conducting clinical trials throughout the EU	
Simplification of safety reporting (single safety reporting for all Investigational Medicinal Products (IMPs)	
Winter clock stop	

ber 23 to January 7, when the timer of procedure temporarily stops, and no due date is allowed to be set during this period for an RFI.[6]

The new regulation is also applicable for national clinical trials, therefore smaller companies and academia which usually perform clinical trials in a single country have the same documentation burden but may cope better with the tight timelines.

The submission package: Why harmonisation really makes sense

THEN: Under Clinical Trial Directive, the general requirements for application of clinical trials with medicinal products was defined in the CT-1 Guidance Document, EudraLex Vol. 10.[7] Still, every EU competent authority had their own recommendations/naming conventions for the submission package. Table 2 shows an example of different national requirements when submitting a clinical trial application to the Health Authority in Austria,[8] Germany,[9] and Belgium.[10] As shown in Table 2, the first column contains an overview of general guidance of the submission package for the application to the competent authority as laid out in the CT-1 Guidance Document. The rows in the table compare the content of the submission package and the naming conventions for the countries mentioned above. For instance, Belgium did not require numbering of the documents which was recommended for Austria and Germany. Those two countries on the other hand requested different document numbering. Interestingly, in the Belgian guidance, the document naming convention is strictly defined.

Every Member State had their own preference for the submission system. In Austria the submission was done via email or EudraLink[11] and some countries such as Belgium and Germany were strict about the submission via Common European Submission Portal (CESP).[12] The national guidelines strictly communicated which portal was acceptable and that the correct submission channel was also essential to receive an approval of the clinical trial application.[10]

NOW: With the EU CTR the clinical trial documentation is applicable for and consistent in all countries. It is divided in two parts – Part I and Part II (see Table 3).[12] The Reporting Member State is responsible for the assessment of Part I and each Member State's Ethics Committee for Part II. The assessment of the documentation is extensively defined in the regulation.[2]

Submission of the application[2]

The application is submitted online via the CTIS, a system that has been programmed and audited by the EMA. The final rollout of the platform and the functionality were confirmed on January 31, 2022, after various delays.

Once the application is submitted, the sponsor can choose one Member state (an EU/EEA country) to be the Reporting Member State (RMS). If there are no objections or concerns, the proposal for RMS is accepted. If the proposed RMS declines, another Member State can step up

Table 2. Comparison/Overview of the European and national guidelines on the application format

CT-Guidance document, EudraLex Vol. 10	National guidance on the application format and documentation for the clinical trial submission (examples):		
General guidance:	**Austria**[8]	**Germany**[9]	**Belgium**[10]
General information	1. General information (cover letter, EudraCT)	01 Cover letter 02 EudraCT (PDF & XML)	• Cover letter • EudraCT (PDF & XML) • Signature • List of the European competent authorities to which the application has been submitted • Copy/summary of scientific advice
Protocol	2. Current version of the protocol, the synopsis, and the signature pages	03 Protocol	• Protocol
Investigator's Brochure	3. Investigator's Brochure	04 Investigator's Brochure	• Investigator's Brochure
Investigational Medicinal Product Dossier (IMPD)	4. Full IMPD, simplified IMPD or Summary of Product Characteristics (SmPC)	05 IMPD	• IMPD • Simplified dossier of the investigational medicinal product • SmPC • Copy of the manufacturing authorisation GMP certificate for biological active substance • Copy of the import authorisation • Viral safety studies • TSE certificates • Labelling examples in the national languages
Additional information	5. Patient Information, the summary of the Paediatric Investigation Plan or the summary of scientific advice	06 Risk-Benefit 07 Non-IMPD 08 GMP 09 Labelling 10 Administrative documents 11 Scientific advice 12 GMO 13 Xenogenic products 14 Other documents 15 Reporting	

Abbreviations: EudraCT, European Union Drug Regulating Authorities Clinical Trials Database

or be appointed.

The first validation of the application takes place within 10 days and the RMS contacts the sponsor to raise relevant validation issues in the form of a Request for Information. Member States have seven days to communicate requests to RMS. No contact from the RMS means that the validation is complete.

Timelines

Timelines are defined for the three different types of application – initial CTA, substantial modification (substantial changes during the study conduct phase, such as protocol amendments, IB updates and others[2]), and Additional Member State Concerned CTA (Add MSC CTA – adding a new member state for a previously approved clinical trial).[13] A procedure can be divided in three stages – validation phase (including RMS selection), assessment phase, and decision phase. RMS selection is only applicable for the initial clinical trial submission. Validation phase is valid for both the initial clinical trial submission and the substantial modification procedure. Assessment phase is valid for all procedure types (see Table 4). Every procedure has strictly defined timelines (see Table 5). An overview of the phases and submission types has been published by the EMA in their CTIS timelines overview

Table 3. Clinical Trial Submission Package according to the EU-CTR

Part I (evaluation by the Reporting Member State (RMS))	Part II (evaluation by Member States' (MSC) Ethics Committee*)
Scientific, quality, and technical aspects • Cover letter • EU Application Form • Protocol • Investigator's brochure • Good manufacturing practice documentation • Investigational medicinal product dossier/ Auxiliary medicinal product dossier • Scientific advice • EU Paediatric Investigation Plan decision • Labelling • Proof of payment	**National and ethical aspects** • Recruitment of subjects • Informed consent form and subject information leaflet • Compensation arrangements • Suitability of investigators and the clinical trial site • Proof of insurance or indemnification • Data protection • Financial agreements

* Each member state can still define/request the documents in Part II

Table 4. Types of application and phases

Application type	Validation	Assessment	Decision
Initial application	RMS selection and validation phase	Assessment (Part I and II)	Decision
Substantial modification	Validation phase	Assessment (Part I and II)	Decision
Additional Member State concerned (Add MSC CTA)[13]	Not applicable	Assessment (Part I and II)	Decision

handbook.[12]

Technical challenges with the new system and what can we do about it

In the *Clinical Trials Highlights* October 2022 issue, [15] the EMA acknowledged that there are certain technical difficulties with the new system.[16] In December 2022, there have been various articles published showing great concern about the functionality and official roll out of CTIS due to technical difficulties.[17,18]

I had the opportunity to participate in projects concerning EU CTR transition as a local point of contact for the competent authority and the clinical study team involved in the submission. My experience has taught me that in any case, especially with the EU CTR, collaboration is the key. If there is an issue with the portal, of course, it is possible to contact the CTIS helpdesk and try to solve the issue as soon as possible. Sometimes the deadlines are too tight

and contacting RMS is the fastest solution. It is important to have a good relationship with all internal and external stakeholders to find solutions to the technical challenges. It is of interest to both sides (EMA's and sponsor's) that the procedure runs smoothly. As stated in the EMA's *Clinical Trial Highlights* publication: "*Technical challenges encountered with the CTIS workflow for some very large multi-Member State CTAs are being managed through workarounds to minimise the impact on applications*".[15] Furthermore, they offer extensive trainings for the users and published a handbook for sponsors to ease the transition to the new CTA process.[19] After all, Rome was not built in a day.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by his employer or EMWA.

Table 5. Short overview of timelines concerning different procedures[6]

Type of application	Duration of the assessment phase	Decision
Initial Clinical Trial Application	Assessment of Part I – up to 45 days (up to 76 days if RFIs are submitted). Assessment of Part II can run in parallel	Up to 5 days
Substantial modification	Part I or Part I & II assessment up to 38 days (up to 69 days if RFIs are submitted). Part II only assessment up to 33 days (up to 64 days if RFIs are submitted)	Up to 5 days
Adding Member State concerned	Depends on the assessment. Part I or Part II assessment up to 47 days (up to 78 days if RFIs are submitted)	Up to 5 days

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References

1. MedTech Europe. Transition periods – medtecheurope [cited 2023 Jan 21]. Available from : https ://www.medtecheurope.org/new-medical-technology-regulations/transition-periods/
2. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance), 2014 Apr 16 [cited 2023 Jan 21]. Available from : https ://eur-lex.europa.eu/legal-content/EN/TXT/PDF/ ?uri=CELEX :02014R0536-20221205&amp ;from=EN
3. EMA. Development of the clinical trials information system – EMA [cited 2023 Jan 29]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system/development-clinical-trials-information-system
4. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34), No. No 596/2009, 2001 Apr 4 [cited 2023 Jan 21]. Available from: https://health.ec.europa.eu/system/

files/2016-11/dir_2001_20_en_0.pdf
5. EMA. Clinical trials information system – EMA [cited 2023 Jan 21]. Available from : https ://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system
6. CTIS Evaluation Timelines. EMA [cited 2023 Jan21]. Available from: https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-sponsor-handbook_en.pdf
7. Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1), Communication from the Commission], 2010 Mar 30 [cited 2023 Jan 21]. Available from : https ://eur-lex.europa.eu/LexUriServ/LexUriServ.do ?uri=OJ :C :2010 :082 :0001 :0019 :EN :PDF
8. BASG. Guidance for the submission and conduct of clinical trials (CT) with medicinal products; 2019 Jul 3 [cited 2023 Jan 21]. Available from: https ://www.basg.gv.at/fileadmin/redakteure/01_Formulare_Listen/I/L_I209_Guidance_CT_submission_en.pdf
9. BfArM. Electronic submission of clinical trial applications; 2013 Apr 15 [cited 2023 Jan 21]. Available from: https ://www.bfarm.de/EN/News/News-from-the-divisions/News-Clinical-Trials/news/ElectronicSubmission.html
10. FAMHP. Guidance for submission of dossiers to the research and development division; 2021 Aug 5 [cited 2023 Jan 21]. Available from: https://www.famhp.be/sites/default/files/Guidance_submission_RD_%20division_V2_final_05082021_4.pdf
11. Eudralink [cited 2023 Jan 21]. Available from: https://eudralink.ema.europa.eu
12. CESP [cited 2023 Jan 22]. Available from: https://cespportal.hma.eu/Account/Login?ReturnUrl=/
13. EMA. Step-by-step guide. How to evaluate an additional clinical trial application. CTIS Training Programme – Module 08; 2022 [cited 2023 Feb 5]. Available from: https://www.ema.europa.eu/en/documents/other/step-step-guide-how-evaluate-additional-msc-clinical-trial-application-ctis-training-programme_en. pdf
14. Debaut V. The EU Clinical Trials Regulation Main Changes and Challenges. Cromsource.com. 2015 [cited 2023 Jan 21]. Available from: https://www.cromsource.com/wp-content/uploads/2015/02/The-EU-Clinical-Trials-Regulation-Main-Changes-and-Challenges.pdf
15. EMA. Clinical Trials Highlights. 2023 [cited 2023 Jan 22]. Available from: https://www.ema.europa.eu/en/documents/newsletter/clinical-trials-highlights-october-2022_en.pdf
16. Troubleshooting session for CTIS. EMA. 2022 [cited 2023 Jan 22]. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-oms-troubleshooting-ctis-users-session-19-october-2022_en.pdf
17. Sharma V. Mandatory use of 'dysfunctional' EU clinical trial portal raises concern in Germany. Pink Sheet. 2022 [cited 2023 Jan 22]. Available from: https://pink.pharmaintelligence.informa.com/PS147430/Mandatory-Use-Of-Dysfunctional-EU-Clinical-Trial-Portal-Raises-Concern-In-Germany
18. Bruckner T. 'Dysfunctional' trial registry threatens drug research across Europe. Transparimed. 2022 [cited 2023 Jan 22]. Available from: https://www.transparimed.org/single-post/ctis-germany
19. Clinical Trials Information System (CTIS) – sponsor handbook. EMA. 2022 [cited 2023 Jan 22]. Available from: https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-sponsor-handbook_en.pdf

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The Lay Protocol Synopsis: Requirements and feasibility

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Abstract

The EU Regulation 536/2014 included a requirement for companies to produce a Protocol Synopsis with a recommendation for a version in lay language. This requirement stated, among other things, a maximum length of two pages. This article outlines the requirements of the regulation with respect to the Protocol Synopsis, and discusses their feasibility in light of the maximum page limit.

In 2014, the EU introduced a new regulation: EU CTR 536/2014.[1] This regulation replaced the previous Clinical Trials Directive 2001/20/EC,[2] and became mandatory with the opening of the Clinical Trials Information System (CTIS) on January 31, 2022. The new regulation was introduced to ensure that the rules for the assessment of clinical trial applications and the conduct of clinical trials were identical throughout the EU. There were many new aspects introduced by the regulation, and as part of the EMA's drive towards transparency and openness, it included requirements for sponsor companies to produce a Lay Summary of Clinical Trial Results, as well as a recommendation for a Protocol Synopsis in lay language.

Both of these requirements have caused much discussion in the industry, because they called upon a completely different writing skill set. For the first time, companies were required to explain complex scientific and clinical information clearly, concisely, without being biased or promotional in any way, and in a manner that is also understandable to the general public. The content requirements of the Lay Summary of Clinical Trial Results are outlined in full in Annex V of the Regulation, but in contrast, the Protocol Synopsis is only mentioned in one line in Annex 1 (D.24), which states simply, "the protocol shall be accompanied by a synopsis of the protocol".

In response to requests for more guidance, the Protocol Synopsis content requirements were discussed in more detail in the latest Question & Answer document (version 6.2), which was issued by the Authority in September 2022.[3] These requirements are extensive and include a maximum page allowance. This article will look at the requirements for the Protocol Synopsis in lay language and discuss if it is feasible to produce the document as required.

What is the Protocol Synopsis?

Quite simply, the Protocol Synopsis is a summary of the main aspects of the protocol, and there is a recommendation from the Authority to produce a version in language that is "understandable to a layperson." The latest guidance does not state what a "layperson" is considered to be, but it does outline the nine sections that should be included in the synopsis, with some description:[3]

1. **EU trial number and full trial title**
2. **Rationale**: Specify the background and hypothesis of the trial.
3. **Objective**: Specify the main and secondary objectives of the trial.
4. **Main trial endpoints**: Describe the main trial endpoints and when they are assessed, e.g. the main trial endpoint is the percent change in the number of events from baseline to a specified time, or the total number of adverse reactions at a particular time after baseline.
5. **Secondary trial endpoints**: Describe the secondary trial endpoints, and when they are assessed, e.g. the number of adverse events until 30 days after the end of treatment.
6. **Trial design**: Describe the design and the expected duration of the trial for the individual subjects, e.g. double-blind, placebo-controlled clinical trial, where subjects are participating for X weeks.
7. **Trial population**: Describe the trial population, indicating the main inclusion criteria, including age and disease/healthy volunteer and the main exclusion criteria to protect the subject, e.g. patients with moderate asthma, 18–55 years, with normal kidney and liver function and without gastrointestinal ulceration or risk factors for a cardiac arrhythmia; healthy volunteers, 18–60 years, who have not been exposed to radiographic examinations during the last 12 months.
8. **Interventions**: Describe interventions and treatment duration, also including background treatment if any, e.g. one group receives a 10 mg tablet of product X twice daily for Z weeks while also receiving product Y as background treatment, and the other group receives a placebo tablet twice daily, as well as product Y. Also describe trial-related diagnostic and monitoring procedures used.
9. **Ethical considerations** relating to the clinical trial, including the expected benefit to the individual subject or group of patients represented by the trial subjects, as well as the nature and extent of burden and risks: A benefit-risk analysis should be done for the trial-specific treatments and interventions, clearly explaining if the trial involves an expected individual benefit (e.g. as required in emergency situations) or a group benefit. When a trial is placebo-controlled, a brief justification should be given. If a non-therapeutic trial is carried out in vulnerable groups, e.g. in minors, incapacitated persons, pregnant or breastfeeding women, their inclusion has to be justified, and it should be explained why the risks and burden are considered minimal and why the trial can only be performed in this particular patient group. The trial-specific risks and burdens for subjects and caregivers (if applicable) related to diagnostic, therapeutic, and monitoring procedures should be justified, e.g. the amount and number of blood samples, the number of site visits, physical examinations, or other tests, as well as any physical and physiological discomfort associated with trial participation.

Furthermore, unlike the Lay Summary of Clinical Trial Results, the Protocol Synopsis has a required maximum page limit of two pages.

Challenges

Aside from the general challenges of writing for the general public (which are outside of the scope of this article), there are a number of specific challenges associated with the Protocol Synopsis requirements as set by the Authority.

There is no guidance about how much background should be given in section 2, or how many secondary objectives should be given in section 3 (the implication being that all of them should be included). The objectives, main, and secondary trial endpoints (which must be described in sections 4 and 5) can be very complex and take a large amount of space to explain in plain language, a problem that is compounded by the requirement to not only describe, but state the timeframe of the assessments. The trial design and population (sections 6 and 7) can also be very complex and potentially confusing, and are often most easily explained using infographics, which can work very well but do take up a lot of space.

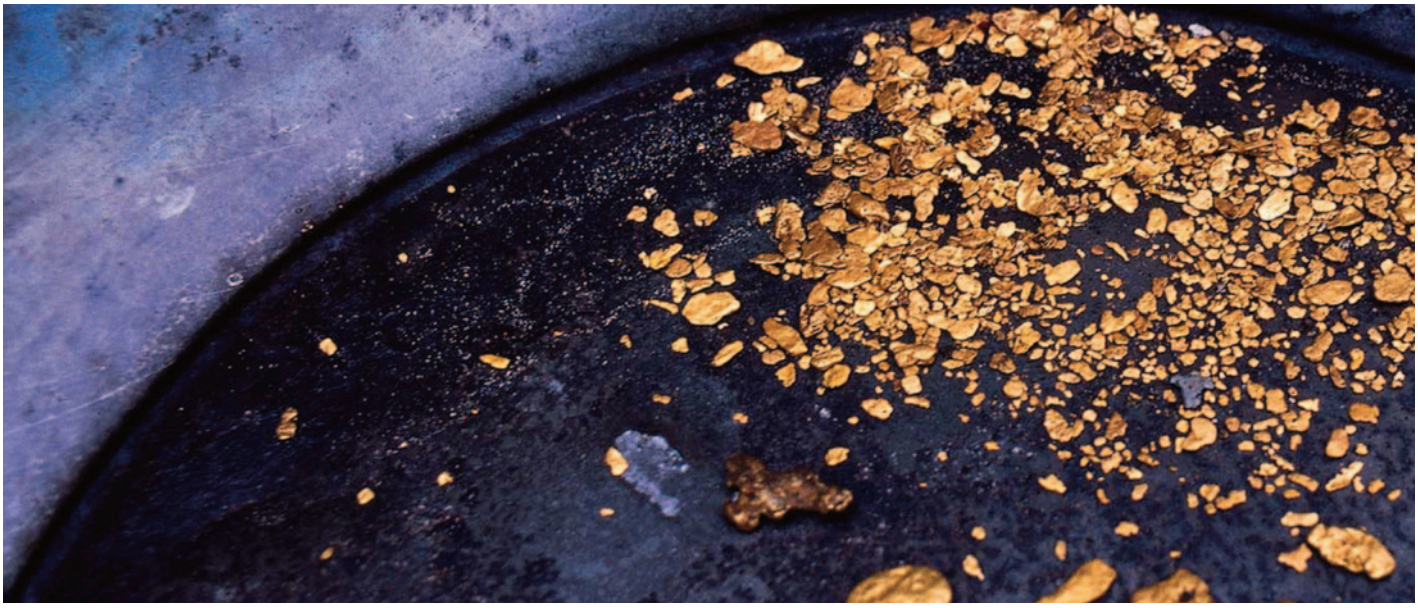
> Quite simply, the Protocol Synopsis is a summary of the main aspects of the protocol, and there is a recommendation from the Authority to produce a version in language that is "understandable to a layperson".

Section 7 also requires the inclusion and exclusion criteria to be described, which can be extensive, involving a lot of complicated clinical and technical terms and assessment criteria. A description of the inclusion and exclusion criteria in clinical regulatory language often takes a page alone (and we must consider that extra words are often necessary to explain concepts in plain language), and the requirement to include a description of the background treatment and trial-related diagnostic and monitoring procedures (section 8) could be extremely lengthy, depending on the therapy area.

Similarly, section 9's requirements for an ethical discussion and a benefit-risk analysis would be extremely challenging to condense into a meaningful, plain-language document.

Conclusions

Considering that the guidance on the requirements of the Protocol Synopsis runs to a page and a half on its own, and that in general, it takes more words (and therefore, more space) to explain complex concepts in plain language, the two-page limit would make a fit-for-purpose document almost impossible to achieve for all but the most simple of studies. This is a great shame (and cause of much frustration) because arguably a plain



language Protocol Synopsis is most needed for more complex studies.

Some companies are ignoring the recommendation completely. Some are exploring the use of a glossary to allow them to circumvent the two-page limit by adding explanations of terms and abbreviations to a separate document. Unfortunately, this not only risks uncoupling the glossary from the main text, but also requires the reader to do quite a lot of memory work and cross-referencing, just to be able to understand the document – surely the opposite of what any plain language document, but especially the Protocol Synopsis, is trying to achieve.

However, the Authority must be applauded for recommending a version of the Protocol Synopsis in lay language. The concept is sound – providing a simplified, easy-to-understand summary of how and why a study was done for the general public is necessary. Additionally, the Protocol Synopsis could and should form a great basis for the Lay Summary of Clinical Trial Results document, and the plain language used in the Informed Consent Form could be brought forward to both documents, thereby minimising effort and simplifying the messaging for the general public.

Surely it would be better to have a three-page Protocol Synopsis that is clear and understandable, than a two-page document that the public cannot understand.

A *suggested* page limit is a very sensible strategy to avoid long, convoluted, unclear documents (whether in plain language or not!), but I fear that having a strict limit disincentivises companies to even try to produce these documents in plain language – the task in many cases is just too daunting, if not unachievable. My hope is that the Authority allows some flexibility on this page limit. Surely it would be better to have a three-page Protocol Synopsis that is clear and understandable, than a two-page document that the public cannot understand.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. EUR-Lex- Access to European Union law [cited 2022 Oct 12]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536.
2. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 [cited 2022 Oct 12]. Available from: https://health.ec.europa.eu/system/files/2016-11/dir_2001_20_en_0.pdf.
3. Update – EudraLex – Volume 10 – Clinical trials guidelines – Questions and Answers Document - Regulation (EU) 536/2014 – Version 6.2 (September 2022) [cited 2022 Oct 12]. Available from: https://health.ec.europa.eu/latest-updates/update-eudralex-volume-10-clinical-trials-guidelines-questions-and-answers-document-regulation-eu-2022-09-26_en.

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Guest Editors: Laura Kehoe and Satyen Shenoy

Lay titles for clinical trials: Is industry achieving the balance?

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Abstract

Titles of clinical trials may directly influence whether patients, caretakers, or healthcare professionals will want to obtain more information about the trial. Major clinical trial registries require lay titles (referred to as "brief" or "public" titles) that are understandable to the public. However, devising adequate lay titles is challenging. In this study, we assessed the quality of lay titles from Phase II/III and III clinical trials registered in ClinicalTrials.gov in 2021. Assessments included the presence of recommended elements, use of technical terms, an expert assessment of adequacy and informativeness, title length, and the use of acronyms. A large proportion (72%) of lay titles did not include all recommended elements, contained technical terms (73%), and were not adequate according to experts (51%). Often, brevity was given precedence over content and understandability. Generally, lay titles with acronyms had better ratings in all assessed categories. These results suggest that industry sponsors can do more to create lay titles that better inform patients and healthcare providers.

Introduction

Titles are the key contact points between readers and authors, and they are the most read part of any article, book, posting, or trial registry entry. Based on the title, readers will decide whether they want to retrieve further information. A title should direct attention, be easy to read, and comprehensively and clearly describe what the main document is about. A title should also be informative to the reader and as specific as possible.[2,3]

This is also true for clinical trials. Titles of clinical trials may directly influence whether patients, caretakers, or healthcare professionals will want to obtain more information about the trial. Because most clinical trial registries return a list of trial titles in response to a search query, the title is the key element in identifying clinical trials that are of interest for patients, caregivers, and healthcare providers.[4]

All registries that contribute to the World Health Organization International Clinical Trials Registry Platform (ICTRP) are required to provide both a scientific title and a lay title for each clinical trial. In many registries, the title displayed in response to a search query is the lay title, referred to as the "public title" by the ICTRP and the "brief title" by ClinicalTrials.gov.

Titles are the key contact points between readers and authors, and they are the most read part of any article, book, posting, or trial registry entry.

The requirement to provide a lay title was originally introduced with the initial release of ClinicalTrials.gov (2008) and with the launch of the ICTRP (2005). Although the requirement has been around for more than 15 years, many sponsors still do not appear to provide easy-to-read and understandable trial titles in their trial registrations. For example, an assessment of patient focus in a representative sample of ClinicalTrials.gov records from 2017 to 2018 showed that brief titles achieved only 52% of the maximum score, indicating that patient focus was underdeveloped.[4] By providing a plain language checklist, ClinicalTrials.gov recently (September 2022) bolstered the use of lay language in trial registry entries such as brief summaries, which intend to provide high-level overviews of clinical trials.[5]

Previously, we analysed the challenges in generating lay titles for clinical trials that are effective at both informing the readers and complying with ClinicalTrials.gov requirements.[6] A well-written lay title is not only easy to read but will also inform the reader about the topic of the

trial, the interventions studied, and the target population. It should also be concise so that it meets formal requirements and increases the likelihood that it will be remembered. Titles also need to be accurate and not mislead the reader about potential benefits of the intervention being investigated.

Lay titles need to be written in language that is understandable for non-specialists, that is, the lay public. This is stated in the ClinicalTrials.gov Protocol Registration Data Element Definitions, which explain that the brief title should be "a short title of the clinical trial written in language intended for the lay public. The title should include, where possible, information on the participants, condition being evaluated, and intervention(s) studied."[7] The limit for brief titles on ClinicalTrials.gov is 300 characters including spaces.

All registries that contribute to the ICTRP are required to provide both a scientific title and a lay title for each clinical trial.

In the current study, we assessed the quality of lay titles for late-phase clinical trials registered in ClinicalTrials.gov in 2021. We focused on late-phase clinical trials because we assumed that they are of particular interest to patients, mainly because they tend to be large, multinational trials that offer a realistic opportunity for participation. Furthermore, late-phase trials often compare an investigational drug with established treatments that patients may already be familiar with. We also considered that late-phase trials would be of particular interest to patients because the safety profile of the investigational substances has already been explored more comprehensively than in earlier-phase trials.

Methods

Data extraction

In February 2022, we extracted lay titles of trials posted on ClinicalTrials.gov during 2021. We focused on industry-sponsored interventional clinical trials in Phase II/III or Phase III. To limit the total number of lay titles to be analysed, we further narrowed the scope to the following therapeutic areas: bowel disease, dementia, chronic kidney disease, and breast cancer. These four search terms were entered in the ClinicalTrials.gov search field. This resulted in a list of 74 lay titles.

Analysis of lay titles

Four experts (i.e. the authors of this article) with 2–7 years (median 6.5 years) of experience in lay language writing and creating lay titles were randomly assigned to rate the lay titles so that each title would be rated by two different experts. The analysis included three categories: presence of recommended elements, presence of technical terms, and an expert assessment on adequacy and informativeness. After completing the assessment, individual scores were compared, with differences resolved by discussion among the experts to achieve a single harmonised score.

Assessment of the presence of recommended elements

The presence of the following recommended elements was assessed: intervention, target population, scientific aim, and condition.[6] Members of the expert panel scored the presence of each required element in the lay title from 0 to 4.

Assessment of the presence of technical terms

It was assessed whether the lay titles included any technical terms. For example, words in Latin language like "versus" or specialised terms like receptor names or mode of action details were considered technical. However, substance name and disease name were not considered to be technical terms (see Table 1). Titles were categorised into the following groups: titles

without technical terms, those including one technical term, and titles with two or more technical terms.

Expert assessment of adequacy and informativeness

Titles were assessed based on the experts' previous experience in the field and were scored as "adequate" or "needs improvement". Titles could be assigned a score of "needs improvement" if they lacked important information, were very complicated, included cryptic terminology, or had grammar problems like unclear pronoun references or unclear sentence structure.

> To be truly helpful, an acronym should relate to the trial, be easy to pronounce and remember, and not be misleading or coercive.

Other assessments

The length of the titles was determined based on the number of characters with spaces and descriptive statistics were calculated. Thereafter, the inclusion of technical terms and recommended elements as well as the expert assessment were analysed for short titles with fewer than 100 characters and longer titles with 100 characters or more.

In addition, the use of trial acronyms was investigated. Lay titles with and without trial acronyms were compared with regards to inclusion of recommended elements, use of technical terms, overall adequacy, and length.

Statistical analysis

Only descriptive analyses were performed. Calculations were made using Microsoft Excel (Version 2202; Microsoft Corporation, Redmond, WA, USA), and figures were prepared using GraphPad Prism (Version 9; GraphPad Software LLC, San Diego, CA, USA).

Results and discussion

Recommended elements

Only 28% of the 74 lay titles included all four recommended elements (intervention, target population, scientific aim, and condition; Figure 1). In other words, 72% of titles were not in line with recommendations. Almost a quarter of the lay titles only included two recommended elements (23%), while another 47% included three recommended elements.

Technical terms

Only 27% of lay titles were free of technical terms, 31% had one technical term, and 42% included two or more technical terms (Figure 1).

The abundance of technical terms is not surprising because they are shorthand for complex content. Lay-friendly expressions are usually longer and do not always cover all aspects of the technical term. However, the inclusion of technical expressions may drastically limit understanding and, hence, the usefulness of a title, particularly for the general public.

It can be challenging for authors of lay titles to determine whether certain terms are "technical" or not. For example, the meaning of some technical terms may be well known to people living with a disease but not to the wider population. Table 1 lists some frequently occurring words and phrases together with the rationale for the experts' assessments of whether they were considered technical terms.

Expert assessment

Each lay title was assessed individually based on the experts' impression and given an overall score. The aim was to have an experience-based assessment of the adequacy and informativeness of the titles. For example, a title with poor grammar would be assessed as not adequate, as would a title that comprised many technical terms or a title with an unclear or missing aim. Based on the experts' assessment, only about half of the analysed lay titles (49%) were considered adequate (Figure 1).

Table 1. Frequently occurring terms in lay titles and whether they are considered technical terms

Term	Frequency	Considered a technical term?	Rationale for assessment
Metastatic/Metastasis	26%	No	Likely to be well known to people living with cancer
Safety and efficacy[a]	26%	Yes	Non-informative; technical terminology whose full meaning is unlikely to be known to non-specialists
Placebo	14%	No	Term is widely known; it is important for potential trial participants to know they may receive placebo
Moderate to severe[b]	9%	Yes	Grading of disease severity is usually conducted by investigators. Their assessment may or may not coincide with that of patients living with a disease, hence, this is a specialist's assessment whose rationale is unclear to most patients.
Versus	8%	Yes	Latin term with confrontational connotations that does not fully reflect the comparison intended by the trial design.
Trial phase	7%	Yes	Unlikely to be understood by non-specialists

[a] Or "efficacy and safety" [b] Or variation of this phrase

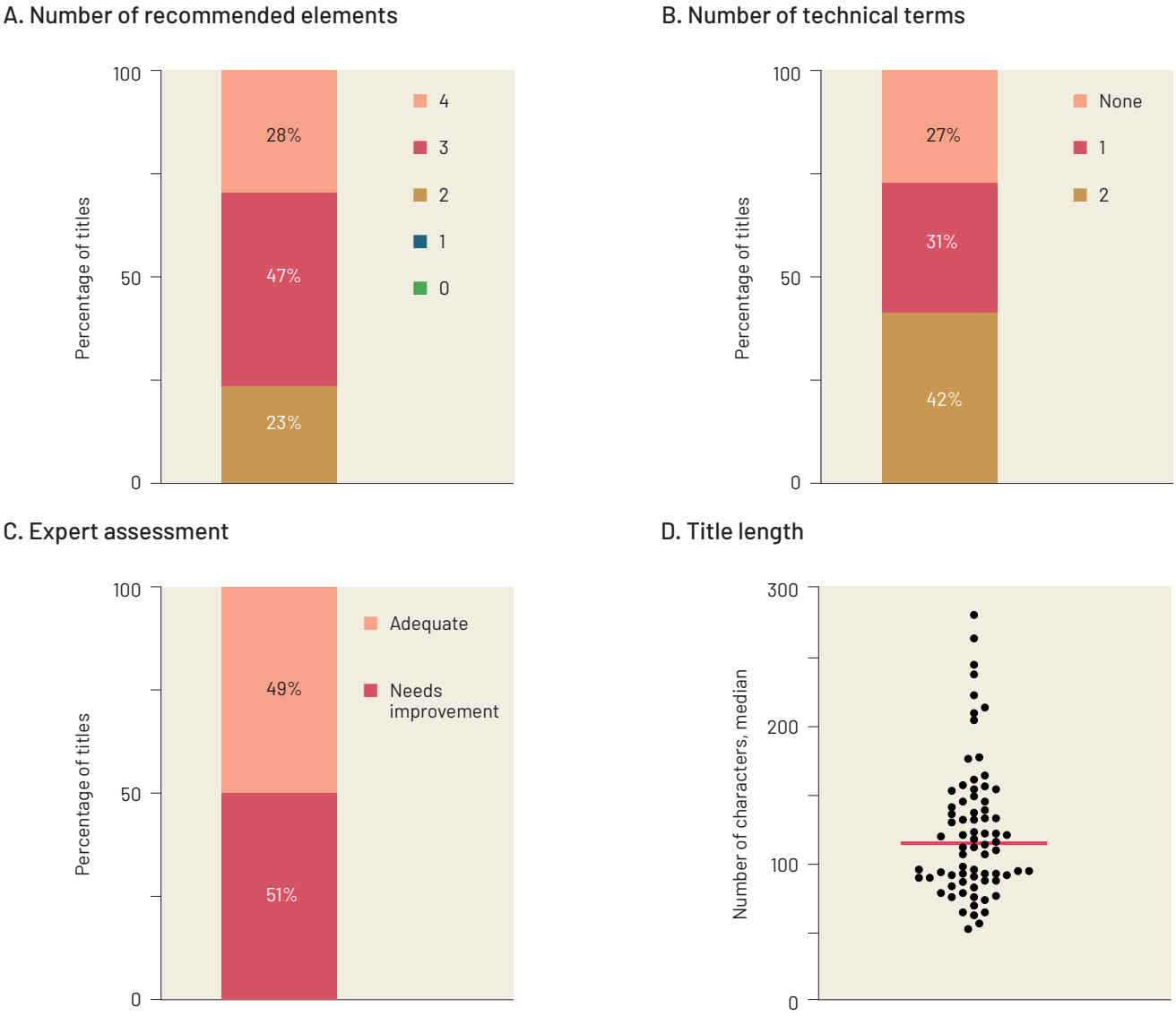


Figure 1. Analysis of lay titles for the (A) number of recommended elements (There were no titles with 1 recommended element and 1 title with 0 recommended elements.), (B) number of technical terms, (C) expert assessment, and (D) length.

Due to rounding, percentages may not add up to 100%.

Length

Sentence length in plain language writing is an important consideration. Various guidelines recommend using short sentences because they are easier to understand. To investigate whether this applies also to lay titles, we asked whether short titles are as effective as longer titles at fulfilling the requirements.

All titles analysed were within the ClinicalTrials.gov-specified maximum of 300 characters including spaces. The longest title was 283 characters and the shortest was 56 characters. The majority of titles (89%) had fewer than 200 characters (Figure 2), while 41% had fewer than 100 characters. The median title length was 118 characters, and the mean length was 127 characters. Our overall analysis of lay titles suggests that an emphasis on brevity comes at the cost of inclusion of recommended elements. All four recommended elements were included in 41% of the titles with 100 characters or more but only 10% of those with fewer than 100 characters. Expert assessment was "adequate" for just over half (55%) of titles with 100 characters or more but for only 40% of those with fewer than 100 characters. Interestingly, titles shorter than 100 characters were more likely to be free of technical terms (37%) than those with 100 characters or more (20%) (Figure 2).

Acronyms

When communicating about a particular trial, it is not very practical to use the full trial title. A shorthand notation or acronym facilitates trial-specific communication and outreach to both healthcare providers and patients. That is one of the reasons why sponsors create trial acronyms to make communication easier and more memorable. Further reasons may be that the trial acronym is an element of branding as some trial acronyms are also used for follow-up trials (e.g. EASE SBS 3, EASE SBS 4). Trial acronyms convey cohesion across the different communication channels, for example, through scientific publications, posters, flyers, and regulatory

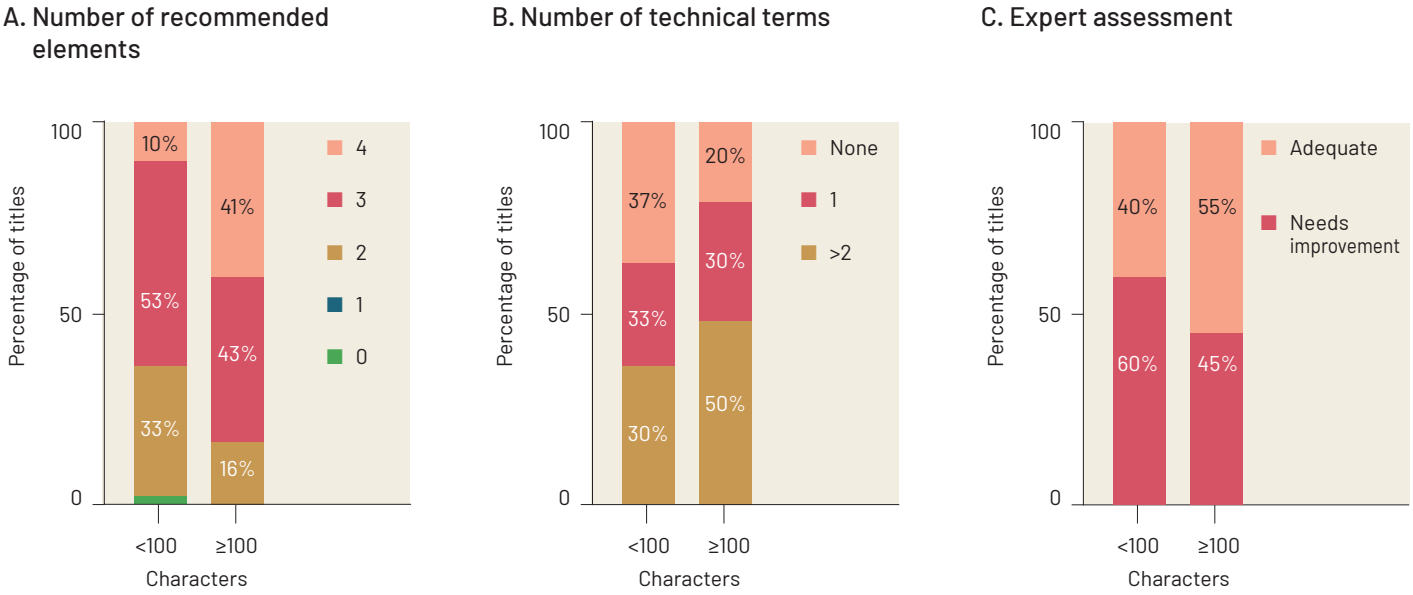


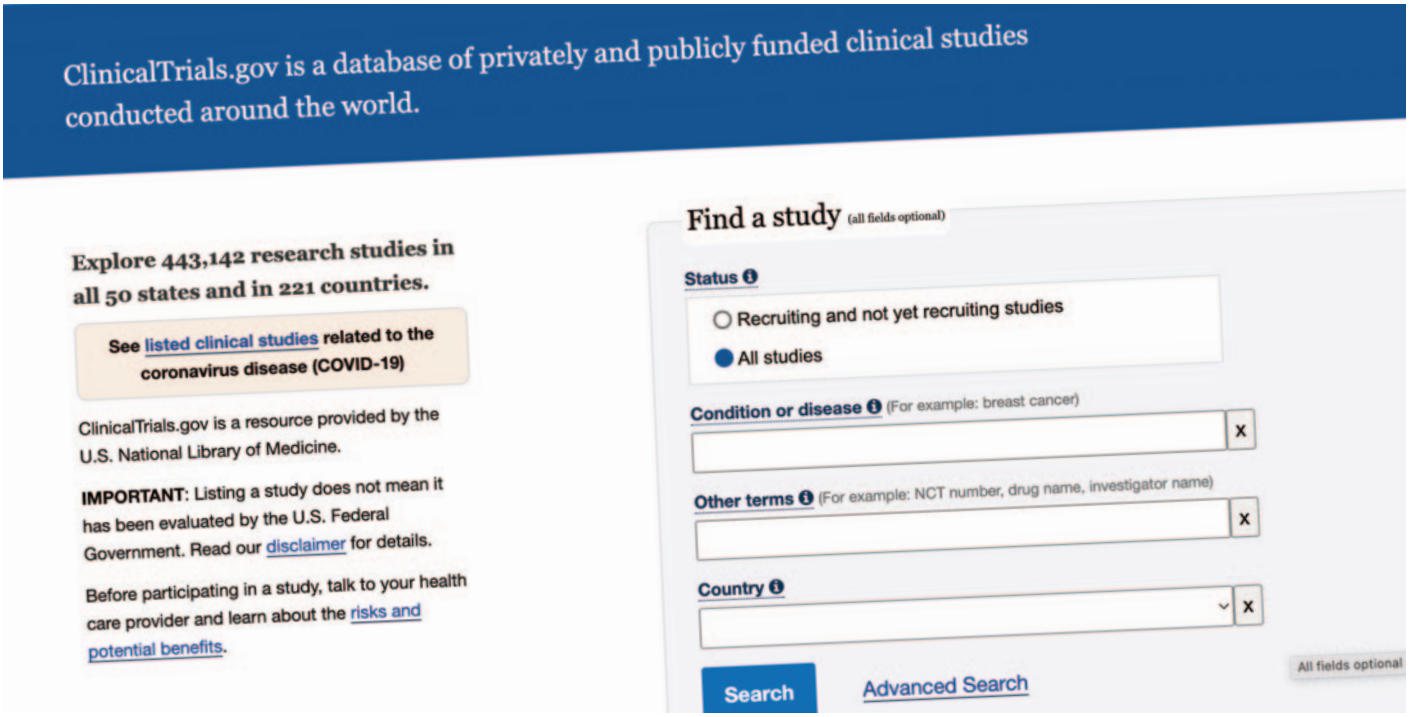
Figure 2. Analysis of lay titles according to length in characters

Lay titles of fewer than 100 and 100 characters or more (including spaces) are compared for the (A) number of recommended elements, (B) number of technical terms, and (C) expert assessment. Due to rounding, percentages may not add up to 100%.

documents such as the Informed Consent Form, Clinical Trial Report, and Lay Summary. However, the use of acronyms is contentious.[8] Positive-sounding acronyms or those that suggest a positive trial outcome can be manipulative and may unduly influence patients' decisions about participation.[9] Currently, there is no regulation on the use of acronyms in clinical trial titles.[10]

In our sample of 74 late-phase lay titles, 43 (58%) contained a title acronym. Overall, seven trials did not enter the acronym into the appropriate field, while 84% of the acronyms were correctly entered. We found that lay titles with an acronym were on average longer, had fewer technical terms, had more recommended elements, and were more likely to be assessed as adequate than those without (Figure 3). One possible reason is that sponsors that choose to develop a trial acronym may be exercising greater care for other trial title attributes and therefore design more lay-friendly titles.

Some of the acronyms in our sample imply a positive outcome of the trial, such as PRESERVE 2, STABILIZE-CKD, EASE SBS 3,



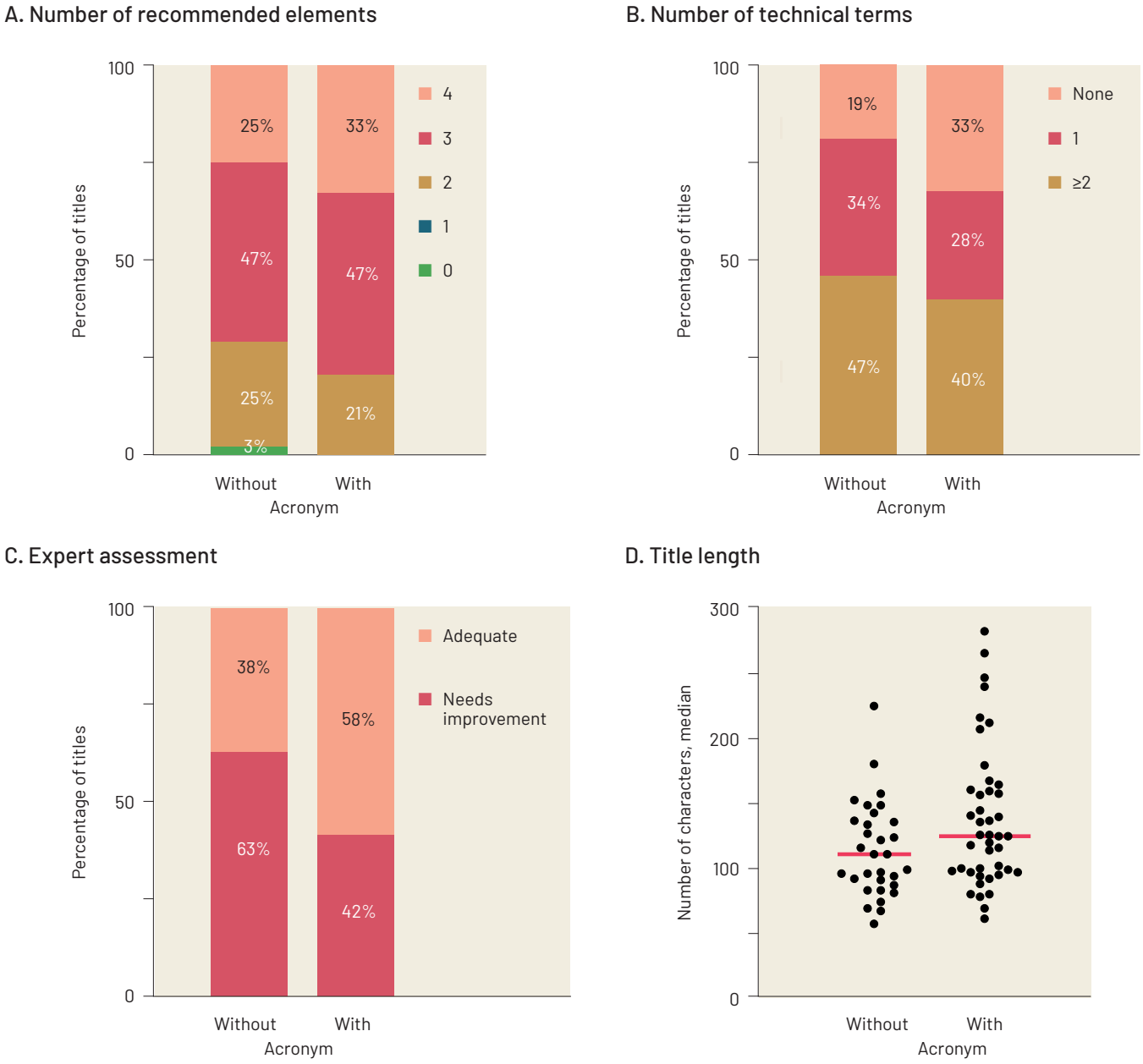


Figure 3. Comparison of lay titles

With and without acronyms for the (A) number of recommended elements, (In the group without acronym, there were no titles with 1 recommended element, and in the group with acronyms, there were no titles with 0 or 1 recommended elements.)(B) number of technical terms, (C) expert assessment, and (D) length. Due to rounding, percentages may not add up to 100%.

CORRECTION, CONVERSION, ELEVAT UC 40 JAPAN, and TRAILBLAZER-ALZ 4. In addition to acronyms that suggest a positive outcome, there are those that can be associated with strength or other positive qualities, such as ENIGMA-SC, ZEUS, EPIK-B5, STARS extend, DESTINY-B12, and ARTEST. Some acronyms seemed to resemble women's names, such as EMBER-3, SERENA-6, KATE3, Astefania, and OVELIA, potentially with the objective of conveying qualities traditionally associated with women: caring, loving, and healing. In OVELIA, the two connotations are even combined, as the name "ovelia" in Greek means "help".

In some cases, the acronyms are constructed so that they phonetically resemble a familiar word or expression but with a different spelling. For example, ARTEST is pronounced as "artist", and EPIK-B5 is pronounced as "epic". Both are associated with positive-sounding, familiar terms. But the different spelling could also cause problems and confusion when searching for a particular trial.

Many acronyms lack a direct link to the disease or the trial. From the acronym alone, it is difficult to know what the trial is about. However, some acronyms include the abbreviation of the disease, the affected organ, or an important gene mutation, such as TROPION-Breast01, STABILIZE-CKD, FIND-CKD, HER2CLIMB-05, TRAILBLAZER-ALZ 3, and TransportNPC. However, the abbreviations included might only be meaningful for people with a certain disease

or for healthcare professionals and not for the general public.

To be truly helpful, an acronym should relate to the trial, be easy to pronounce and remember, and not be misleading or coercive.

Conclusion

Our analysis suggests that industry sponsors have not yet realised the potential of good, comprehensive, and understandable lay titles for their clinical trials. While many titles are very short (<100 characters), this brevity comes at the cost of important details about the trial. Lay titles often include technical terms that may not be understood by potential trial participants. Furthermore, well-designed acronyms may be helpful for trial-identification and communication. Overall, industry sponsors are yet to achieve the optimal balance between length, level of detail, and readability in trial titles for lay audiences.

Disclosures and conflicts of interest

The authors are employed by Boehringer Ingelheim Pharma GmbH & Co. KG or BioNTech SE. However, the views expressed in this article are those of the authors and do not necessarily reflect those of their employer or EMWA.

Data availability statement

For inquiries about data and other supplemental information, please contact the corresponding author.

References

1. Why the title of your paper matters. Nat Hum Behav. 2021;665:5. doi:10.1038/s41562-021-01152-2
2. Schultz DM. Eloquent science: A practical guide to becoming a better writer, speaker and scientist. Chapter 3: Writing an effective title. 2nd ed. Boston (MA): American Meteorological Society; 2009.
3. Grant MJ. What makes a good title? Health Info Libr J. 2013;30:259–60.
4. Schindler TM, Grieger F, Zak A, et al. Patient preferences when searching for clinical trials and adherence of study records to ClinicalTrials.gov guidance in key registry data fields. PLoS ONE. 2020;15(5):e0233294. doi:10.1371/journal.pone.0233294
5. ClinicalTrials.gov. "What's New", Sept 26, 2022 [accessed 2022 Dec 5]. Available from: https://clinicaltrials.gov/ct2/about-site/new
6. Leithold LHE, Brown CM, Schindler TM. Lay titles for clinical trials: A balancing act. Med Writ. 2018;27(2):55–8.
7. ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies (01 October 2020) [cited 2022 Nov 29]. Available from: https://prsinfo.clinicaltrials.gov/definitions.html.
8. Berlin L. TAC: AOITROMJA? (The acronym conundrum: Advancing or impeding the readability of medical journal articles?). Radiology. 2013;266(2):383–7. doi:10.1148/radiol.12121776
9. Meirson T, Markel G, Bomze D. The common sense behind clinical trial names: An empirical study of trial acronyms. Account Res. 2022;29(7):460–73. doi:10.1080/08989621.2021.1951254
10. Washington HA. Limning the semantic frontier of informed consent. Journal of Law, Medicine & Ethics. Cambridge University Press; 2016;44(3):381–93.

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The September 2023 edition

Automation/Software

Streamlined complex medical report writing supported by artificial intelligence/machine learning is making its way into clinical regulatory writing. The medical writing automation's goal is to speed up and ease clinical development processes by reducing the time and cost involved in creating and keeping regulatory documents up to date. This issue will examine current issues, challenges, and opportunities towards human guided medical writing automation systems.

Guest Editors: Shiri Diskin and Daniela Kamir

To bias or not to bias in oncology clinical trials: Perspectives on design, endpoint selection, and reporting

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Abstract

Developing drugs for cancer is a process as complex as the disease itself. At the planning stage of a clinical trial for an oncology drug, thorough and careful consideration must be given to choosing the right study design and endpoints/estimands, as any bias introduced at the outset of the clinical trial would cascade down to the analysis and eventually the reporting of the results. The common study designs for oncology drugs, their challenges, the current perspectives (and dilemmas) in the industry on choosing the right endpoints/estimands, design and reporting biases, and the roles of medical writers in facing these challenges are discussed in this article.

Almost 20 million new cancer cases with nearly 10 million deaths were estimated in 2020.[1] Cancer is one of the leading causes of death globally, and consequently, research and development of oncology drugs has never lost its momentum. Between 2009 and 2020, the US FDA approved over 300 oncology drugs (excluding supportive medicines).[2] Between 2010 and 2019, 85 marketing authorisation applications of oncology drugs in Europe received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP).[3] Although Europe appears to be falling behind the US in terms of regulatory approval speed of oncology drugs,[4] we see a soaring number of approvals in both regions every year. Conducting an oncology clinical trial from planning to reporting is a painstaking process. The fact that there are multiple guidances dedicated for different tumour types in oncology clinical trials alone shows the magnitude of the complexity of drug development for cancers.

Study designs of oncology trials

Marketing approval of oncology drugs is the culmination of years of research accumulating substantial, confirmatory evidence of efficacy and safety of the investigational drugs acquired from "adequate and well-controlled clinical trials".[5] This refers to trials that have a valid control for comparison to quantitatively assess the drug's effect, appropriate eligibility criteria for the target population, a robust randomisation method, proper masking of participants/observers/data analysts, well-defined and reliable study endpoints, and sound data analytical methods.[5]

For confirmatory studies, proving superiority of an investigational drug to the control on clinically meaningful endpoints in a randomised, controlled, blinded setting is arguably the standard and is considered the most reliable design to demonstrate efficacy.[6,7] The control used in such studies can be a placebo, active comparator, or both. Data of a superiority study is relatively easy to interpret and for drawing inference of efficacy when superiority of the investigational drug to the control is demonstrated.

When an active control is compared with the investigational drug to establish efficacy, a noninferiority design could be applied to show that the treatment effect difference between the investigational drug and the active control is not beyond a prespecified minimum margin.

Some important considerations, often also considered as challenges, when applying a noninferiority trial design include:[8]

1. The active control must have a well-characterised effect;
2. The treatment effect size of the active control and the minimum margin are determined from reliable historical data;
3. An appropriately powered sample size should be determined based on the expected treatment effect of the investigational drug and the active control;
4. The noninferiority hypothesis and method of statistical test should be chosen carefully.

> Confirmatory evidence of efficacy and safety of the investigational drugs must be acquired from "adequate and well-controlled clinical trials".

In a randomised setting, the cross-over design either allows patients of all treatment arms to be switched over to the opposite arms or patients from one treatment arm to another treatment arm that shows benefit. The latter is typically applied in oncology trials when patients taking placebo experience disease progression, for ethical and patient accrual reasons. Nevertheless, the cross-over design in oncology trials is considered to pose more risks than it does in non-oncology studies, such as symptomatic treatment of chronic diseases and single-dose pharmacokinetic/pharmacodynamic studies, as it often confounds the study endpoints beyond the point of cross-over.[9,10] Meticulous planning to include cross-over design in an oncology trial is imperative to avoid misinterpretation of the efficacy data down the line.

Certain circumstances require special attention, such as when no active therapy is available, meaning that using a placebo as control is ethically unfeasible, or when the available patient pool is limited (e.g. for rare diseases), a single-arm study design may be acceptable to assess drug efficacy. Justification, however, is needed for choosing a single-arm design as it presents inherent drawbacks which may limit the validity of the efficacy data and its generalisability, e.g. difficulties in assessing causality of adverse events, lack of comparison data to ascertain the real effect of the

treatment, and restricted sample size and endpoints selection.[7]

Endpoints selection

In the past, new cancer drugs were typically approved based on tumour assessment outcomes, which are considered surrogate endpoints, such as the tumour objective response rate (ORR), duration of response (DOR), progression free survival (PFS), and time to progression (TTP). For several decades, regulatory authorities across regions have been of the unanimous opinion that Phase 3 confirmatory oncology trials should demonstrate direct evidence of clinical benefit from the investigational drug, that is to extend survival and improve quality of life, and these are intended as the basis for marketing approval.[6,7,11] Therefore, overall survival (OS) and a selected patient-reported outcome (PRO) such as health-related quality of life (HRQoL) have been the "gold standard" for efficacy assessment of new oncology therapies.[12-15] Each clinically meaningful and surrogate endpoint presents its own advantages and disadvantages, which are nicely summarised in the FDA guidance (Table 1).[6,14]

An estimand framework to underpin any Phase 3 confirmatory trial design, including oncology trial design, is necessary.[16] In the absence of reference to estimands in other oncology trial design guidances, the examples relating to oncology trials within the E9(R1) addendum on estimands and sensitivity analysis are helpful.[16] These include:

1. A subject switching treatment in an oncology trial as an intercurrent event (ICE) for which the clinical question of interest must be clear and appropriate strategies for addressing this event be applied. Helpfully, Manitz et al.[17] has recently reported an estimand framework for OS in oncology trials with treatment switching.
2. When certain clinical oncology events may represent ICEs of which occurrence or non-occurrence would define different populations of interest. This could occur for time-to-event endpoints. The estimand framework for some of these types of ICEs are elucidated further in recent publications.[18,19]
3. When an ICE to an original endpoint in itself is informative about the patient's outcome, for example, treatment discontinuation could be considered part of PFS and incorporated into the definition of PFS. Casey et al.[20] have described the estimand framework to support composite outcomes in the oncology setting.

An estimand framework to underpin any Phase 3 confirmatory trial design, including oncology trial design, is necessary.

With the emergence of real-world evidence, improved knowledge on the omics of cancer, and new transformative therapeutics that have changed the natural histories of certain cancer types, discussion has ensued in the past decade about reassessing the endpoints in oncology trials for marketing approval.[21,22] While preserving their standpoint on the importance of clinically meaningful endpoints, regulatory authorities acknowledge the potential benefits of new

*Table 1. Advantages and disadvantages of important cancer approval endpoints**

Endpoint	Advantages	Disadvantages
Overall survival	• Easily and precisely measured • Generally based on objective and quantitative assessment	• May be affected by switch-over of control to treatment or subsequent therapies • Needs longer follow-up • Includes noncancer deaths
Symptom endpoints (patient-reported outcomes)	• Generally assessed earlier and with smaller sample size compared with survival studies	• Blinding is important for assessing the endpoint • Potentially subject to assessment bias, particularly in open-label studies • Lack of validated instruments in many disease areas • Definitions vary among studies • Balanced timing of assessments among treatment arms is critical
Disease-free survival or event-free survival	• Generally assessed earlier and with smaller sample size compared with survival studies • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Balanced timing of assessments among treatment arms is critical • Includes noncancer deaths
Objective response rate	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumour attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Frequent radiological or other assessments • May not always correlate with survival
Complete response	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumour attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Frequent radiological or other assessments • May not always correlate with survival
Progression-free survival or time to progression	• Generally assessed earlier and with smaller sample size compared with survival studies • Measurement of stable disease included • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Balanced timing of assessments among treatment arms is critical • May not always correlate with survival

* This table is taken from the US FDA Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry. https://www.fda.gov/media/71195/download

treatment modalities based on surrogate endpoints and the need to make these treatments rapidly available to cancer patients with serious or life-threatening conditions. The catch is that evidence must be available to justify the ability of the surrogate endpoints to predict clinical benefit.[23,24] For example, what is the probability that patients showing delayed progression for an indicated cancer type (prolonged PFS) will also show improved survival (prolonged OS)? Indeed, an increasing number of oncology drugs were approved based on surrogate endpoints and up to half of these were through accelerated approval, with ORR and PFS as the most common primary endpoints.[25-30] For drugs that obtain accelerated approval, drug companies are required to fulfil the obligation to continue to provide post-marketing efficacy data to verify the anticipated clinical benefit.

Counterarguments against the overuse of surrogate endpoints for marketing approval are equally extensive. For a start, valid evidence for the chosen surrogate endpoints to predict long-term OS or QoL is generally lacking and if

available, is restricted to a specific tumour type such as advanced colorectal and ovarian cancers.[31,32] Consequently, most approved oncology drugs based on surrogate endpoints did not prove clinical benefit. Eighty-six percent of identified FDA approvals based on surrogate endpoints from 2008 to 2012 either failed to verify long-term OS or no such data were reported at all;[26] 58% of FDA approvals from 1992 to 2019 did not report any post-marketing efficacy data at all, and for new approvals, more than half had no or poor correlation between the surrogate endpoints and OS.[30] Similarly, 49% of European Medicines Agency (EMA) approvals from 2009 to 2013 did not show benefit on OS or QoL.[33] These reports prompt a couple of questions: are cancer patients still gaining the clinical benefit that they hope they will gain from their therapies? Are regulatory authorities doing enough in overseeing drugs that are approved based on surrogate endpoints to protect the interest of public health?

To validate a surrogate endpoint, the Institute of Medicine Committee proposed a 3-step evaluation process:[34]

1. Analytical validation – to assess if the surrogate endpoint itself can be accurately measured;
2. Qualification – to assess if the investigational drug affects both surrogate and clinical endpoints in a like manner;
3. Utilisation – to assess the context of the proposed use of the surrogate endpoint.

> With the emergence of real-world evidence, improved knowledge on the omics of cancer, and new transformative therapeutics … discussion has ensued in the past decade about reassessing the endpoints in oncology trials for marketing approval.

It is painstaking but crucial to discern a validated surrogate endpoint with robust estimated net effects of a drug on a clinically meaningful endpoint from a mere correlate without any established evidence of clinical benefit.[32,35,36]

Biased by design

How confident are we to say that a trial is "adequate and well-controlled" when it is claimed to be randomised, controlled, and blinded? We may naturally take the credibility of a randomised, controlled, and blinded trial for granted and miss subtle design details that could bias the trial. Bias can occur at any stage of a randomised clinical trial, from setting of the clinical question at the ideation of the trial, design and conduct, data management and analysis, to final data reporting.[37] Bias arising from inappropriate study design at the outset of a clinical trial would cascade all the way down to the outcome of results and therefore the reporting. Eventually, inference of the results in reporting is likely to be misguided by the distorted results and may

Table 2. Common design biases in randomised controlled studies and their impacts on the study outcome

Design characteristics	Types of bias	Impact on outcome
Objective	Multiple primary endpoints, multi-arm	Results in multiple comparison, hence exaggerating the drug effects and increasing the false-positive rate.[42]
Treatment allocation	Inappropriate inclusion of cross-over design	Confounding factor for the drug's effect on survival from the point of cross-over.[37]
Randomisation method	Inadequate allocation concealment/ sequence generation (e.g. open random allocation schedule, lack of safeguarding of assignment envelopes)	• Imbalance group sizes and baseline characteristics, hence unequal comparison between treatment arms. • Drug effect estimates were larger by 10% to 17% in studies with inadequate versus adequate allocation concealment.[43-45] • Drug effect estimates were larger by 7% in studies with inadequate versus adequate sequence generation.[45]
Blinding	Lack of (double-) blinding	Drug effect estimates were larger by 7% to 13% in unblinded versus blinded studies.[43,44]
Choice of control	Use of control with distinct safety profile, dose modification regimen	Unequal comparison between investigational drug and control.[37]
Analysis method	• Inappropriate handling of missing data and choice of analysis population • Excluding patients from analysis	• Drug effect estimates were larger by 17% when using modified intention-to-treat (mITT) in place of intention-to-treat (ITT).[46] • Drug effects were more beneficial in studies with patient exclusion versus no exclusion.[47]

undermine regulatory decision-making. Table 2 describes several common design biases in randomised controlled studies and their impacts on the study outcome, including drug effect estimates.

Not considering estimands in the study design would also amount to a design bias. For Phase 3 confirmatory oncology trials, ICEs should be defined and the appropriate strategies for addressing these ICEs should be determined according to the clinical questions of interest at the outset. One should be aware that using different strategies for the same ICE would address different questions.[20] A well-designed estimand framework will reduce the risks of missing data, help address the right question, ensure appropriate analyses, and eventually support the interpretation of the results.

Reporting bias

In addition to "passive" reporting bias due to biases in the design choices, "active" reporting bias has been the kind of bias that medical writers would consciously avoid, albeit not always successfully. The most common reporting biases include:[38-40]

1. Publication bias – not publishing clinical trials with negative outcomes;
2. Outcome reporting bias – reporting only the favourable data or a subset of data, or even changing the primary endpoint in reporting;
3. "Spin" – strategising the reporting to emphasise the benefit of the investigational drug even though it is not supported by the hypothesis testing.

In an analysis of the reporting of randomised controlled studies for breast cancer, one fifth of studies reported in ClinicalTrials.gov had the primary endpoint altered in the final report; one-third of the studies were reported to have positive outcome by "spinning" the results to focus on other endpoints; and half of the studies were reported to have a positive outcome based on a non-statistically significant test result for the primary endpoint.[39] These staggering statistics may only represent the tip of the iceberg.

The implications of reporting bias, passive or active, could be profound for the oncology drug development industry and public health sector. Incomplete and skewed reporting of outcome results could mislead policymakers in drug approval decision-making, thereby misinforming medical service providers, and potentially jeopardising access to effective treatments for cancer patients.

> Bias can occur at any stage of a randomised clinical trial.

What can we do as medical writers?

- **Be proactive and do it the right way from start to finish.** Myriad guidelines, for generic study types and oncology trials alike, are available to help us from planning and design all the way to accurate and transparent reporting.[41] If we are involved in planning the research strategy, be encouraged to engage with the regulatory authorities to discuss the best study design based on the nature of the disease, availability of comparators, known benefit-risk of the investigational drug, and the long-term plan for collecting data on the clinical benefit of the drug.
- **Equip ourselves with the right knowledge.** Be vigilant and learn where to look. Is the comparator appropriate? Do the study endpoints fit the study design and answer the clinical question? What is the expected magnitude of clinical benefit? Does a Phase 3 confirmatory trial design include some kind of estimand framework? If not, open discussions with the medical expert and biostatistician. Being able to identify biases throughout the entire clinical trial will help us report the trial critically and clearly.
- **Remember that responsibility for appropriate trial design does not rest solely with the medical writer.** We may need to raise awareness where it might otherwise be lacking, but ultimately, design considerations and responsibilities lie with the sponsor, medical expert, and biostatistician.
- **Be aware of the different types of reporting biases.** Understanding the types of reporting biases, under what circumstances they may happen, and their implications in clinical research will help us all to become more "conscious" writers.

> The most common reporting biases include publication bias, outcome reporting bias, and "spin".

Conclusion

Writing for oncology trials is never an easy task. Challenges await at every stage of a clinical trial, from ideation to reporting. Medical writers need to equip themselves with solid knowledge of the oncology drug development process, be attentive to new treatment modalities in oncology, be conscious of the current trends in oncology trial designs, be aware of the possible biases in all aspects of a trial, and be skilled to tackle the biases, all of which are essential for clear and transparent writing. Appropriate oncology trial design can and should be advocated for by a well-informed medical writer, but must be a cross-functional endeavour, at a minimum involving the sponsor, medical expert, and biostatistician. Fortunately, myriad resources exist to help medical writers at every stage of the writing process – perhaps that is yet another challenge to locate the right resource for the right purpose.

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The opinions expressed in this article are the author's own and not necessarily shared by her employer or EMWA.

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References

1. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: Cancer Today. Lyon: International Agency for Research on Cancer; 2020 [cited 2022 Nov 9]. Available from: https://gco.iarc.fr/today.
2. Olivier T, Haslam A, Prasad V. Anticancer drugs approved by the US Food and Drug Administration from 2009 to 2020 according to their mechanism of action. JAMA Netw Open. 2021;4(12):e2138793. doi:10.1001/jamanetworkopen.2021.38793
3. Garsen M, Steenhof M, Zwiers A. A decade of marketing authorization applications of anticancer drugs in the European Union: An analysis of procedural timelines.

Ther Innov Regul Sci 2021;55:633–642. doi:org/10.1007/s43441-021-00260-5
4. Lythgoe MP, Desai A, Gyawali B, et al. Cancer therapy approval timings, review speed, and publication of pivotal registration trials in the US and Europe, 2010-2019. JAMA Netw Open. 2022;5(6):e2216183. doi:10.1001/jamanetworkopen.2022.16183
5. US FDA. 21 CFR 314.126(b) [cited 2022 Nov 10]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.126.
6. US FDA. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry Dec 2018 [cited 2022 Nov 11]. Available from: https://www.fda.gov/media/71195/download.
7. EMA. Guideline on the Clinical Evaluation of Anticancer Medicinal Products. EMA/CHMP/205/95 Rev.6. Jan 05, 2019. [cited 2022 Nov 11]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf.
8. US FDA. Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry. November 2016 [cited 2022 Nov 11]. Available from: https://www.fda.gov/media/78504/download.
9. Haslam A, Prasad V. When is crossover desirable in cancer drug trials and when is it problematic? Ann Oncol. 2018 May 1;29(5):1079–81. doi:10.1093/annonc/mdy116.
10. Prasad V, Grady C. The misguided ethics of crossover trials. Contemp Clin Trials. 2014 Mar;37(2):167–9. doi:10.1016/j.cct.2013.12.003. Epub 2013 Dec 21.
11. Center for Drug Evaluation, China Food and Drug Administration. Technical Guidance for Cancer Drug Clinical Trials Endpoints. May 15, 2012 [cited 2022 Nov 15]. Available from: https://www.cde.org.cn/zdyz/domesticinfopage?zdyzIdCODE=24d174aa6995cf17e7aa12d6aa0317aa.
12. Roila F, Cortesi E. Quality of life as a primary end point in oncology. Ann Oncol. 2001;12 Suppl 3:S3-S6. doi:10.1093/annonc/12.suppl_3.s3
13. Pazdur R. Endpoints for assessing drug activity in clinical trials. Oncologist. 2008;13 Suppl 2:19–21. doi:10.1634/theoncologist.13-S2-19
14. Driscoll JJ, Rixe O. Overall survival: still the gold standard: why overall survival remains the definitive end point in cancer clinical trials. Cancer J. 2009;15(5):401–5. doi:10.1097/PPO.0b013e3181bdc2e0
15. Delgado A, Guddati AK. Clinical endpoints in oncology – a primer. Am J Cancer Res. 2021 Apr 15;11(4):1121–31.
16. EMA. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials [cited 2022 Nov 20]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf.
17. Manitz J, Kan-Dobrosky N, Buchner H, et al. Estimands for overall survival in clinical trials with treatment switching in oncology. Pharm Stat. 2022;21(1):150–62. doi:10.1002/pst.2158
18. Bornkamp B, Rufibach K, Lin J, et al. Principal stratum strategy: Potential role in drug development. Pharm Stat. 2021;20(4):737–51. doi:10.1002/pst.2104
19. Fiero MH, Roydhouse JK, Bhatnagar V, et al. Time to deterioration of symptoms or function using patient-reported outcomes in cancer trials. Lancet Oncol. 2022;23(5):e229–e234. doi:10.1016/S1470-2045(22)00021-3
20. Casey M, Degtyarev E, Lechuga MJ, et al. Estimand framework: Are we asking the right questions? A case study in the solid tumor setting. Pharm Stat. 2021;20(2):324–34. doi:10.1002/pst.2079
21. Jones DS, Podolsky SH. The history and fate of the gold standard. Lancet. 2015;385(9977):1502–3. doi:10.1016/S0140-6736(15)60742-5
22. Blumenthal GM, Kluetz PG, Schneider J, et al. Oncology drug approvals: Evaluating endpoints and evidence in an era of breakthrough therapies. Oncologist. 2017;22(7):762–7. doi:10.1634/theoncologist.2017-0152
23. US FDA. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. May 2014. [cited 2022 Nov 20]. Available from: https://www.fda.gov/media/86377/ download.
24. EMA. Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004. 23 July 2015 [cited 2022, Nov 20]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-scientific-application-practical-arrangements-necessary-implement-regulation-ec-no/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf.
25. Downing NS, Aminawung JA, Shah ND, et al. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. JAMA. 2014;311(4):368–77. doi:10.1001/jama.2013.282034
26. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: An analysis of 5 years of US Food and Drug Administration approvals. JAMA Intern Med. 2015;175(12):1992–94. doi:10.1001/jamainternmed.2015.5868
27. Beaver JA, Howie LJ, Pelosof L, et al. A 25-year experience of US Food and Drug Administration accelerated approval of malignant hematology and oncology drugs and biologics: a review. JAMA Oncol. 2018;4(6):849–56. doi:10.1001/jamaoncol.2017.5618
28. Kordecka A, Walkiewicz-Żarek E, Łapa J, Sadowska E, Kordecki M. Selection of endpoints in clinical trials: trends in European Marketing Authorization practice in oncological indications. Value Health. 2019;22(8):884–90. doi:10.1016/j.jval.2019.03.007
29. Naci H, Davis C, Savović J, et al. Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of cancer drugs by European Medicines Agency, 2014–6: cross sectional analysis. BMJ. 2019;

366:l5221. Published 2019 Sep 18. doi:10.1136/bmj.l5221
30. Chen EY, Haslam A, Prasad V. FDA Acceptance of surrogate end points for cancer drug approval: 1992-2019. JAMA Intern Med. 2020;180(6):912–4. doi:10.1001/jamainternmed.2020.1097
31. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol. 2012;30(10):1030–3. doi:10.1200/JCO.2011.38.7571
32. Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? BMC Med. 2017;15(1):134. doi:10.1186/s12916-017-0902-9
33. Davis C, Naci H, Gurpinar E, et al. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ. 2017;359:j4530.
34. Institute of Medicine (US) Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease. Perspectives on Biomarker and Surrogate Endpoint Evaluation: Discussion Forum Summary. Washington (DC): National Academies Press (US); 2011.
35. Fleming TR. Surrogate endpoints and FDA's accelerated approval process. Health Aff (Millwood). 2005;24(1):67–78. doi:10.1377/hlthaff.24.1.67
36 Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. Stat Med. 2012;31(25):2973–84. doi:10.1002/sim.5403
37. Prasad V, Berger VW. Hard-wired bias: How even double-blind, randomized controlled trials can be skewed from the start. Mayo Clin Proc. 2015 Sep;90(9):1171–5. doi: 10.1016/j.mayocp.2015.05.006.
38. Kirkham JJ, Altman DG, Williamson PR. Bias due to changes in specified outcomes during the systematic review process. PLoS One. 2010;5(3):e9810. doi:10.1371/journal.pone.0009810
39. Vera-Badillo FE, Shapiro R, Ocana A, et al. Bias in reporting of end points of efficacy and toxicity in randomized, clinical trials for women with breast cancer. Ann Oncol. 2013;24(5):1238–44. doi:10.1093/annonc/mds636
40. Mitra-Majumdar M, Kesselheim AS. Reporting bias in clinical trials: progress toward transparency and next steps. PLoS Med. 2022;19(1):e1003894. doi:10.1371/journal.pmed.1003894
41. MacCarthy A, Kirtley S, de Beyer JA, et al. Reporting guidelines for oncology research: helping to maximise the impact of your research. Br J Cancer. 2018 Mar 6;118(5):619–28. doi:10.1038/bjc.2017.407.
42. Othus M, Zhang MJ, Gale RP. Clinical trials: design, endpoints and interpretation of outcomes. Bone Marrow Transplant. 2022;57(3):338–42. doi:10.1038/s41409-021-01542-0
43. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study BMJ 2008; 336:601 doi:10.1136/bmj.39465.451748.AD
44. Savović J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Ann Intern Med. 2012;157(6): 429–38. doi:10.7326/0003-4819-157-6-201209180-00537
45. Page MJ, Higgins JP, Clayton G, et al. Empirical evidence of study design biases in randomized trials: Systematic review of meta-epidemiological studies. PLoS One. 2016;11(7):e0159267. doi:10.1371/journal.pone.0159267
46. Abraha I, Cherubini A, Cozzolino F, et al. Deviation from intention to treat analysis in randomised trials and treatment effect estimates: meta-epidemiological study. BMJ. 2015;350:h2445. doi:10.1136/bmj.h2445
47. Nuesch E, Trelle S, Reichenbach S, et al. The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study BMJ 2009; 339:b3244 doi:10.1136/bmj.b3244

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We all know there is nothing trivial about clinical trials.

This issue of *Medical Writing* says it all.

But let's have some light fun and try answering the short quiz below.

Answers on page 65

1. What is the earliest documentation of a trial?
2. What is the largest pre-approval trial in terms of number of participants? The smallest?
3. What is the longest running trial?
4. What is the most expensive trial?

I hope you enjoyed this quiz and this MEW issue. Thank you to all our contributors and the editorial team – Editor

The unique challenges of clinical trials in rare disease: A regulatory writer's perspective

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Abstract

Designing clinical trials in rare diseases comes with a specific set of challenges including limited knowledge around the natural history of a disease, small sample size available for trial participation, regulatory guidance that is not calibrated to the rare disease context, manufacturing and supply issues, and safety and financial risks. Here, we discuss some of these potential challenges and how, through proactive early engagement with key opinion leaders, regulatory bodies, and patient groups, a cohesive and strategic clinical development plan can be created to provide the strongest foundations when marketing approval is sought.

Introduction

Clinical trial design is inevitably complex in any context, but in a rare disease with a paediatric population, the task can seem insurmountable. The EMA defines a disease as "rare" if it affects less than 5 in 10,000 of the EU general population.[1] Although individual rare diseases may affect fewer than 100 patients, collectively it is estimated that over 30 million people in the EU live with a rare disease, of whom 30% are children who will die before the age of 5.[1,2] It is estimated that only 6% of all known rare diseases have available treatments, highlighting the need for new therapies.[2]

It is widely acknowledged that industry, academia, regulators, healthcare providers, and others need to collaborate to meet this need for new therapies, but the drug development and trial process is complex with ethical, scientific, operational, and regulatory considerations. Here, we describe some of the key challenges and propose proactive solutions with the aim of getting new, safe, and efficacious treatments to patients with significant unmet medical needs.

Regulatory interaction and incentives

Development of drugs for the treatment of rare diseases carries more financial risks compared with mainstream drug development; A smaller population entails a higher rate of study failure (as every patient has numerically and statistically more impact on results) and less opportunity for returns and recovery of drug development costs. Recognising this, the EMA and European Commission offer "orphan designation" to incentivise companies to develop rare disease treatments.[3]

Currently, if awarded orphan designation, companies benefit from free protocol assistance and 10 years of market exclusivity on approval. A further incentive of an additional 2 years of market exclusivity is awarded to companies who include results of paediatric studies for a medicine with orphan designation. As a sidenote, it is anticipated that orphan drug designation classification requirements and rewards are under review with draft guidance anticipated in 2023.

To qualify for orphan designation, the company must demonstrate that the condition is "rare", that the condition is life-threatening or chronically debilitating, and that the medicine is of significant benefit to those affected by the condition. Establishing these can be challenging, and companies often must get creative using deep data mining techniques and extensive literature searches to find the data required.

Designing a clinical trial

A number of crucial issues must be considered in designing a successful clinical trial, especially in a rare disease population.

What is the objective?

When deciding on the objective of a trial, it is important to consider the bigger picture of the drug development plan (and how the trial fits within the overall drug development plan) and to design a trial with an eye on the ultimate goal, which may be a marketing authorisation application. The next step is defining what the trial is intended to address: "What are you hoping to show?" and "Why does it matter?" This could be a demonstration of superiority in comparison with standard of care, non-inferiority in comparison with standard of care, or simply gaining a greater understanding of the natural history of the disease.

Undoubtably, planning the study design and objective(s) requires an understanding of the natural history of the disease, the disease pathology, and the competitive landscape. Unfortunately, for many rare diseases, little research exists and the diseases are frequently not well-characterised, which means that finding relevant literature and source materials can be challenging. Additionally, competitors are often non-existent. Consequently, engaging in close collaboration with patients, patient advocacy groups, specialist healthcare professionals, and subject matter experts is important to ensure that the objective(s) for the trial is clinically meaningful to patients in a "real-life" context.

Once these objectives are defined scientifically, it is important that the company reaches out to the EMA to validate and confirm the adequacy and acceptability of the proposed objectives from a regulatory standpoint for the study.

Patient population

The patient population selected for the pivotal clinical trials should be representative of the therapeutic indication for the product's planned marketing authorisation and product label, so it

is vital to get this correct from the outset for the potential success of the trial. Selecting the wrong population can also impact recruitment, which in turn can negatively affect the duration of the study.

A fine balance is needed when considering the patient population for a clinical trial: The inclusion and exclusion criteria need to be wide enough to enrol the maximum number of patients without being so general that too much variability (or "noise") is introduced that can dilute the results.

Putzeist reports that failure to identify the most appropriate target population was a key feature of failed orphan marketing authorisations, emphasising the criticality of identifying the appropriate patient population from the start of clinical development.[4] The patient pool is limited in rare disease; Therefore, careful definition of the population is key.

Setting inclusion and exclusion criteria can be tricky with rare diseases as they are typically not well characterised due to lack of available natural history data and a limited in-depth knowledge of the underlying disease pathology. Additionally, given that these diseases often disproportionally affect children, the situation becomes more complex. It is also to be considered that different countries follow different national guidance on diagnosis and treatment, and if the planned trial involves a non-standard parameter in the inclusion and exclusion criteria, it can affect recruitment of both investigators and patients who feel that participation is burdensome.

Choice of study design

The message from EMA is clear on expectations around study design: "Most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials (RCTs) that follow generally accepted rules and guidance." However, the EMA does acknowledge that "a comparative trial will usually be preferable but may not always be possible".[5]

An RCT is well-recognised as the gold standard for an unbiased evaluation of effects to support marketing approval. In an RCT, patients are randomised (usually 1:1) to two (or more) groups to test a new drug compared with placebo or standard or care. An endpoint (defined as "an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial") is measured at specific time points and the results are compared between groups; any differences are tested statistically. This is the ideal design that any pivotal trial should use to gain an unbiased estimate of benefit and risk.

Unfortunately, a clear limitation of RCTs in a rare disease is a smaller number of available potential patients. To support a successful EMA Marketing Authorisation, rare disease pivotal studies may enrol as many as several hundred of patients or as few as less than 30 patients, dependent on the specific disease. This is in contrast to typical RCTs for diseases that are not considered rare, which must enrol more patients for adequate statistical powering and demonstration of significant differences between treatments.

An additional concern with rare diseases is that, even within one specific condition, there is often considerable clinical, mutational, and phenotypical variability between patients, which can complicate interpretation of results.

Innovative adaptive study designs, use of historical controls, and alternative statistical approaches may be acceptable if they help improve the interpretability of the study results. One recommended approach is the use of a cross-over design where patients receive one treatment, followed by a washout phase, and then receive the other treatment. However, this results in a longer trial with two treatment periods, which can raise significant ethical concerns in progressive irreversible diseases and can impact patient recruitment and retention.

Types of controls

The ICH E10 guidance provides direction on the choice of control groups in clinical trials and outlines different options: 1. placebo, 2. no treatment, 3. different dose/regimen of study drug, 4. different active treatment, or 5. external (historical).[6] Options 1 through 4 are concurrent controls (control and test groups are chosen from the same population and treated concurrently).

Option 1 The use of a placebo is generally optimal, as it allows the clearest demonstration of benefit and risk of a treatment. However, this can be problematic as patients with rare diseases are often children who are gravely ill and do not want to take the gamble that they may be randomised to a treatment that has zero therapeutic benefit. In this situation, either a cross-over design (placebo followed by active or vice versa) or an open-label period after a placebo period can prove highly effective as patients are 100% guaranteed to receive active drug.

Option 2 (no treatment) presents an alternative approach. In a no-treatment-controlled trial, patients are randomised to either study drug or no treatment; however, bias can be introduced as it is not possible to blind the investigator and patients and subjectivity becomes a concern.

A useful approach in this type of study is to include a blinded panel of assessors to permit an objective independent evaluation of outcome measures, but it does not solve the inherent possible bias of any patient-assessed outcome. This option can also provide useful data on the natural history and progression of a disease, which is often a relative unknown in many rare diseases.

Option 3 (different dose/regimen of study drug) presents with similar practical and ethics issues as Option 1 where either a placebo or an active-control group is included.

Option 4 (different active treatment) can, generally, be disregarded with rare diseases given that only 6% of rare diseases have treatment options available.[2]

Option 5 (external control [including historical control]) is an interesting alternative that has recently gained a lot of attention within the rare disease world. Specifically, a "virtual" control is formed from patients with the same disease from sources such as ongoing patient registry studies, medical records, and control populations from previous trials. This allows a company to compare their treatment effects essentially against standard of care and/or natural disease progression. However, this approach needs to be used with great caution at the design, analysis, and interpretation stages. To avoid bias, the definition of which patients to include must be tightly controlled to ensure that only patients with very similar disease states, demographics, and medical history are used in the control group.

It is also important to consider that if the study involves a specific efficacy outcome measure, patients in the control group may also need to have data available from that assessment. This can be challenging if the outcome measure is not commonly used, which is a common problem with rare diseases where diagnostic and treatment approaches vary enormously. Despite the potential obstacles of using real-world evidence, the EMA has shown willingness to accept studies with historical controls, but it is crucial to validate this approach with the EMA upfront before conducting the study as it has clear limitations and can impact in terms of future marketing authorisation.[5]

Selection of endpoints

In general, in any kind of trial, including those conducted in rare disease, monitoring of safety through incidence and frequency of adverse events (alongside other safety parameters) form a key endpoint for assessment of benefit/risk of study drug. An efficacy endpoint can be defined as "an event or outcome that can be measured objectively to determine whether the intervention being studied is effective".[7] Alongside the primary endpoint (essentially the measurement tool that is predefined as the main way of answering the question the trial poses), secondary and exploratory endpoints can be crucial to demonstrate the overall benefit in diseases that are less well categorised and should be carefully selected.

In rare diseases, disease-specific clinical endpoints often do not exist due to the limited patient population and lack of natural history data. If disease-specific clinical endpoints do exist, they are frequently unvalidated, not well recognised, or not commonly used in the clinic. Reaching out to patient groups to help understand what endpoints are meaningful for patients is important and, crucially, will support the overall patient benefit claim when seeking marketing authorisation.

In addition to direct clinical outcomes, if available, companies should consider patient-reported outcomes, surrogate (indirect measurement of effect) endpoints, and biomarker analyses that can be linked to clinical benefit to satisfy both EMA requirements and the unmet medical need in patients. It is noteworthy that both surrogate endpoints and biomarker analyses have been used, albeit at times with controversy, to successfully gain conditional (provisional) marketing authorisation for orphan drugs in the EMA.

To this end, it is crucial to get agreement from EMA on endpoint selection and validation as early as possible in the clinical development programme. Fortunately, EMA has recognised this obstacle and companies can request an opinion on the acceptability of a novel biomarker as an endpoint or the use of a surrogate endpoint. Early engagement ensures documented agreement between the EMA and the company that the selected endpoints will provide suitable efficacy data to support marketing approval at a later stage.

Other considerations

Engaging the patient community

Dialogue with patients and patient advocacy and alliance groups is crucial as it allows real-world information to be collected and identifies what improvements would be seen to be significant in the eyes of those experiencing the disease first hand. Importantly, this dialogue begins to establish the process of building trust with the rare disease patient advocacy community. Individuals living with rare diseases may be wary of a healthcare system that is often ill-equipped to diagnose and treat them; Some may have gone through numerous providers, procedures, misdiagnoses, and treatments before even receiving the correct diagnosis. Therefore, to maximise patient compliance and adherence to a clinical trial regimen (and eventually to the approved treatment), companies are well-advised to invest in establishing a relationship with the patient community that is founded on trust.

Geographic dispersion of patients, sites, and investigators

In rare disease, to find the patients, first you must find the treating physicians and convince them to be investigators on your trial. Finding investigators with specialisation in a rare disease can be challenging, and resources such as the Orphanet database, the European Organisation for Rare Disease, and the National Organization for Rare Disorders can aid greatly with this process.[8–10] Investigators can also be found by looking at who participated in previous trials, disease key opinion leaders, and internet/literature searches. It is important to consider when identifying sites and investigators that compliance with global healthcare standards and Good Clinical Practice (GCP) vary around the world. Trials must be GCP-compliant, and outreach and audits to assess this are critical to ensure safety of patients and veracity of data collected. It is inevitable that the more sites, the more challenges arise, and

engagement of local expert contract research organisations aids cultural, linguistic, and procedural differences.

Study drug manufacture and formulation

Planning drug manufacture, supply, and management in rare disease trials presents unique logistical challenges, and selection of an experienced logistics contract research organisation or partner is key.

Orphan drugs are often extremely expensive to manufacture as specialist facilities and equipment are required; Thus, they are initially produced in very small quantities, sometimes even at the individual patient-level. Once safety and efficacy are initially shown and Phase 3 trials are planned, the scale up process begins to ensure enough drug is available. This may involve generation of a commercial "Phase 3" formulation that can be produced faster and more efficiently than the initial formulation. However, this comes with associated requirements such as relative bioavailability studies to show the new formulation is comparable to the preliminary formulation. Notably, as the clinical development programme progresses, it may be necessary to develop and test formulations for specific populations (eg. paediatrics and patients with difficulties swallowing).

Conclusions

Orphan drug development is a hugely expanding area but is undoubtably challenging with no conventional roadmap to follow. Through proactive early engagement with key opinion leaders, regulatory bodies, and patient groups, a cohesive and strategic clinical development plan can be created to provide the strongest foundations when marketing approval is sought.

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The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA.

Disclosures and conflicts of interest

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References

1. EMA. Orphan medicines in the EU. 2020 [cited 2023 Jan 23]. Available from: https://www.ema.europa.eu/en/documents/leaflet/leaflet-orphan-medicines-eu_en.pdf
2. EURODIS Rare Diseases Europe. European Health Data Space: Unlocking the potential of health data for rare disease. 2022 [cited 2023 Jan 23]. Available from: https://www.eurordis.org/ european-health-data-space/#:~:text=There%20are%206000%20various%20rare,rare%20diseases%20have%20curative%20treatment.
3. EMA. Orphan incentives. Amsterdam: The Agency [cited 2023 Jan 23]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/orphan-incentives
4. Putzeist M, Heemstra HE, Garcia JL, et al. Determinants for successful marketing authorisation of orphan medicinal products in the EU. Drug Discov Today. 2012;17 (7–8):352–8.
5. EMA, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical trials in small populations. London: The Agency; 2006 Jul 27.
6. EMA. ICH Topic E 10 Choice of Control Group in Clinical Trials. Step 5: Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). London: The Agency; 2001 Jan.
7. National Cancer Institute at the National Institutes of Health. NCI Dictionary of Cancer Terms. U.S Department of Health and Human Services [cited 2023 Jan 23]. Available from https://www.cancer.gov/publications/dictionaries/cancer-terms
8. Orpha.net. Paris: INSERM [cited 2023 Jan 23]. Available from: https://www.orpha.net/consor/cgi-bin/index.php
9. rarediseases.org. Quincy, MA: National Organization for Rare Disorders (NORD) [cited 2023 Jan 23]. Available from: https://rarediseases.org/
10. Eurordis.org . EURORDIS-Rare Diseases Europe [cited 2023 Jan 23]. Available from: https://www.eurordis.org/

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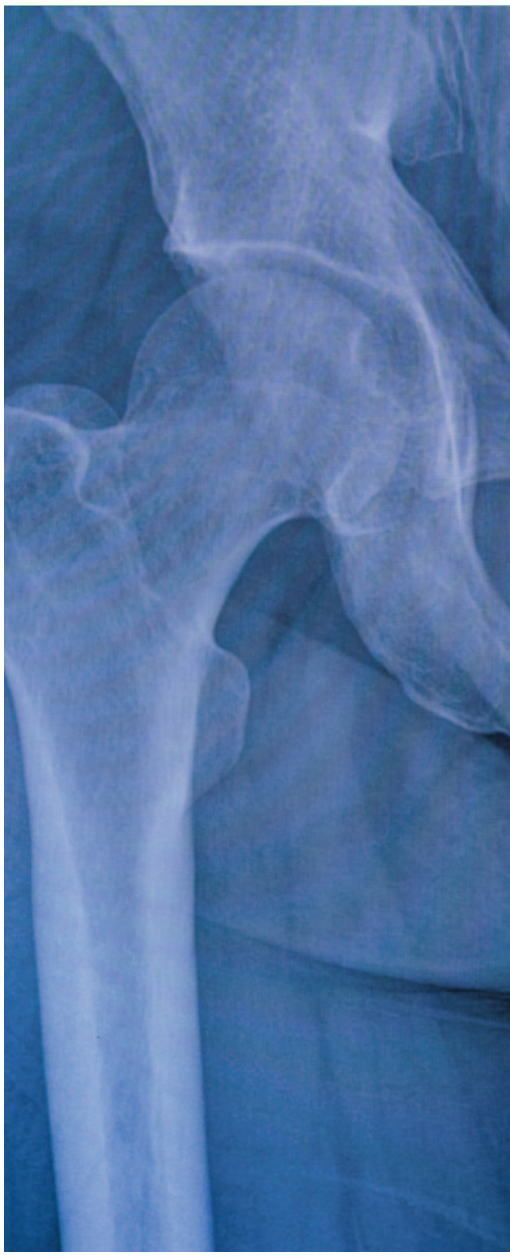
Clinical investigations for medical devices



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Abstract

This article focuses on the medical device specific aspects of clinical investigations and does not aim to be a comprehensive introduction to clinical trials. We highlight the key differences to clinical studies of medicinal products in the context of regulatory requirements in Europe, and discuss which documents are connected to the Clinical Investigation Plan. Finally, we discuss the different types of clinical investigations and the current status of the Clinical Investigation and Performance Studies module of EUDAMED (European Database for Medical Devices).

Introduction

Ten years ago, regulations governing the medical device industry were less strict than for the pharmaceutical industry, and clinical study documents for medical devices were mostly written by project managers. With the publication of the MedDev 2.7/1 Rev 4 guidelines on Clinical Evaluations[1] came greater stringency, and medical device companies became increasingly aware of the medical writing profession.[2] With the implementation of the new EU Medical Device Regulation 2017/745[3] (MDR) came an exponential increase in the demand for medical device writers, even if initially only for writing Clinical Evaluation Reports (CER). Meanwhile, many medical device companies have understood the added value of professional medical writers and now also enlist them to write Clinical Investigation Plans (CIP) and Clinicial Investigation Reports (CIR).

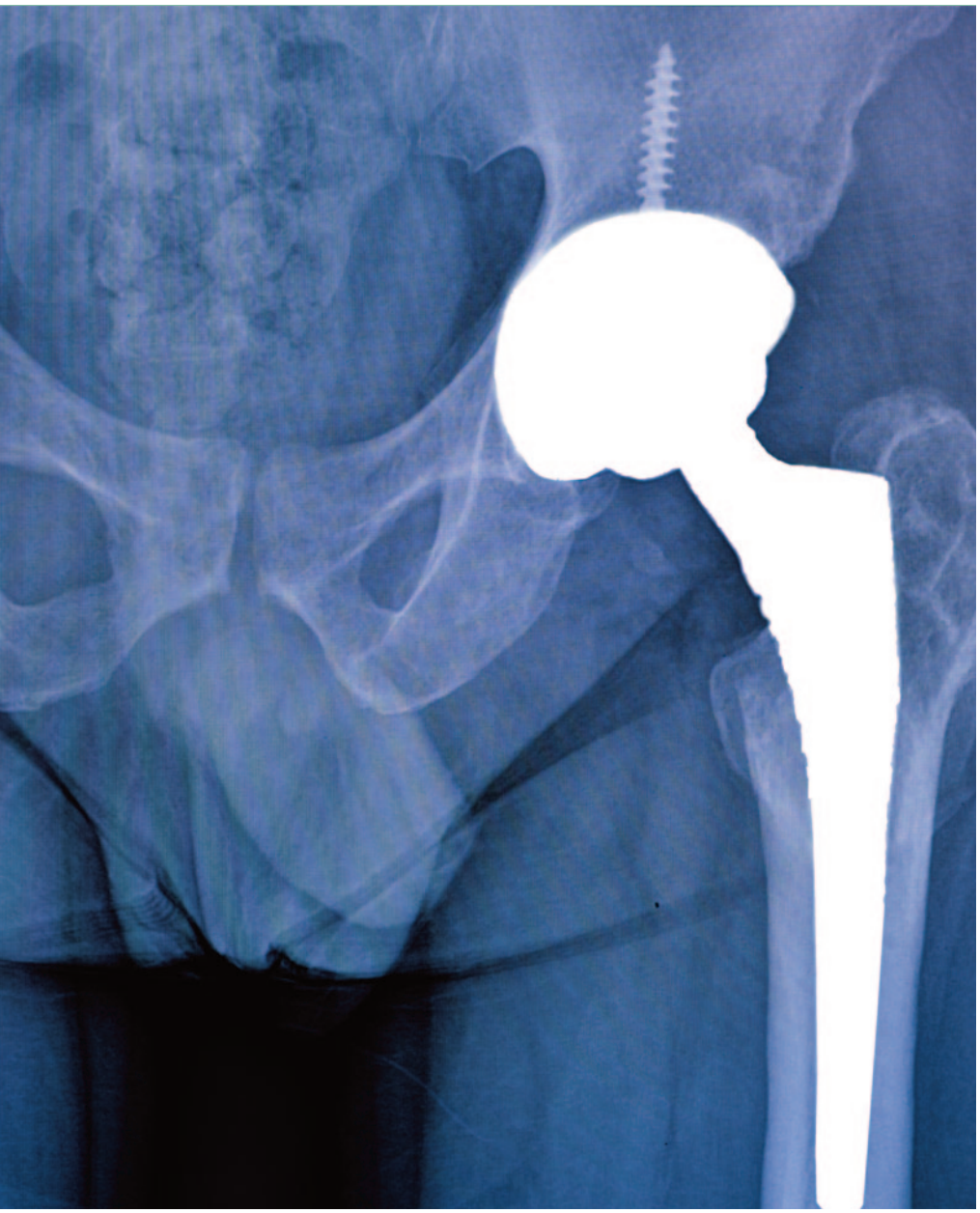
This article aims to familiarise writers with the medical device field and focuses on the medical device specific aspects of clinical investigations rather than broadly encompassing the subject of clinical trials. We further aim to provide a deeper understanding of clinical investigations for writers who work on other medical device documents to help them to put clinical investigation outcomes into context. We focus on Europe, but most aspects of this article are applicable to other regions as well.

Medical devices vs. medicinal products

In our opinion, the most relevant differences are as follows:

- Medical device trials are called "Clinical Investigations" rather than "Clinical Studies" or "Clinical Trials."
- There are no phase I trials in healthy volunteers. In low-risk class devices such as plasters, no clinical investigations are needed. In high-risk classes such as surgical implants, interventional procedures in healthy volunteers would be unethical.
- The clinical investigation design is associated with the risk class of the device. As mentioned above, a clinical investigation might not be necessary for devices classed as low risk. Previously, clinical data were often not needed for moderate-risk devices; though with the release of MDR 2017/745, there is an increasing requirement for clinical data for many such devices, which fosters the need for clinical investigations and hence the need for medical writers. However, the requirements in terms of clinical investigations are often less demanding than for high-risk class devices. Also, if a device is only temporarily used, the clinical investigation follow-up is usually only 30 days to cover procedure-related events, whereas for clinical trials with implantable devices, the follow-up period usually spans over several years.
- For completely novel devices with novel implantation techniques, it is difficult to know what to expect in terms of outcomes and complications, as data from animal studies are only partly translatable into clinical practice, and implantation techniques might be refined along the way.
- Another important difference is that the outcomes in clinical investigations are operator-dependent when an interventional or surgical procedure is involved. For instance, one can imagine that in the case of artificial hip joints, the success of the

> Outcomes in clinical investigations are operator-dependent.



intervention clearly depends on the surgeon. This should be borne in mind when designing, analysing, and interpreting a clinical investigation.

- Likewise, in the case of a novel surgical or interventional technique, there may be a learning curve involved. Consideration may therefore be given to the inclusion of roll-in patients in the CIP in such cases to cover at least part of the learning curve.
- With respect to the analysis of different populations, these are also more complex in the case of medical devices. Consider an investigation with an implantable device. What "what if" questions could be raised? In which group would a patient belong in whom the procedure was started but abandoned? In which group would a patient belong who had the device explanted? Would their follow-up be different from that of other patients?
- In contrast to pharmaceutical clinical trials, where an event is deemed as drug-related or not, an adverse effect that occurs in a patient with a medical device may be device-related or procedure-related. This is relevant since the device itself could work well, but the associated procedure could be too complicated for some surgeons. For example, when transfemoral transcatheter heart valves were developed, the initial antegrade access route was too complicated, so the procedure was adapted to use retrograde access instead.
- Also important is that device deficiencies may occur, which need to be recorded even if they did not necessarily result in adverse outcomes as they might have led to adverse outcomes if circumstances had been less fortunate.
- There are fewer possible interactions with the body in the case of medical devices compared to medicinal products that can interact with body systems at the molecular level. Consequently, clinical investigations of medical devices often need comparatively fewer patients.
- Blinding is more difficult in medical device investigations as the devices often differ in design, therefore often only single-blinded trials are possible, blinding the patients and eventually the core laboratory and clinical events committee to the treatment. Furthermore, placebo-controlled trials (sham procedures[4]) are very rare.
- Medical device companies are, on average, smaller than pharmaceutical companies. The effect of this difference is that the medical writer often has greater influence and more frequently contributes to strategic insights when writing the CIP for a medical device than when writing a Clinical Trial Protocol on behalf of a large pharmaceutical company with standardised document development and highly specialised roles.

For more details on the differences between writing for medical devices and medicinal products, please refer to the articles by Mallia and Walter[5] and Billiones and Thomas.[6]

Applicable regulations

Table 1 provides a non-exhaustive list of the main regulations and guidelines that are relevant for clinical investigations in Europe. In other regions, other regulations may apply such as the US 21 Code of Federal Regulations or Japan's Ministerial Ordinance on Good Clinical Practice for Medical Devices.

Documents related to clinical investigations

A CIP describes how a clinical investigation is conducted, the statistical analysis plan prespecifies the statistical analysis that will be performed, and the informed consent form summarises the clinical investigation for the patient. At the end of the clinical investigation or at specific time intervals, a CIR (final or interim

Table 1. Main regulations and guidelines relevant for clinical investigations in Europe

Declaration of Helsinki[6]	The Declaration of Helsinki is a set of ethical principles. It applies to medicinal products and medical devices.
ISO14155: 2020[7]	Clinical investigation of medical devices for human subjects - Good clinical practice. This ISO document is similar to ICH-GCP E6 for medicinal substances. Its annexes include content requirements for Clinical Investigation Plans, Clinical Investigation Reports, and Investigator's Brochures and provide an overview of different clinical investigation types.
MDR 2017/745[3]	European Medical Device Regulation that mainly describes how to bring medical devices to market and how to ensure their safety and performance. It provides details in terms of clinical investigations and its Annex XV is fully dedicated to clinical investigations.
MDCG guidance documents[8] **MEDDEV guidance**[9]	MDCG guidance documents are continuously developed (a regular check of the website is recommended), and supersede MEDDEV guidance documents. MDCG guidance documents cover several aspects of clinical investigations (application, modification, safety reporting), as well as the associated documents, such as Post-Market Follow-Up Plan and Report, etc.
Local regulations	Local regulations must also be respected, e.g. the Medical Device Act in Germany[10]
Disease specific guidelines, e.g., Academic Research Consortium guidelines[11]	Disease-specific guidelines shall also be respected when designing clinical investigations, e.g., for device trials in coronary interventions, the Academic Research Consortium guidelines provide harmonised definitions for endpoints in clinical investigations.

Abbreviations: ICH-GCP, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Good Clinical Practices; MDCG, Medical Device Coordination Group

report) is created. A beginners' guide to writing CIPs and CIRs for medical devices has been published recently by Jessica Norberg.[13]

The clinical investigation is an instrumental part of the clinical evaluation of the device (except for low-risk devices where a clinical investigation might not be necessary). It derives content from several other documents, and in turn becomes a reference for updates to those documents. The non-exhaustive Figure 1 below is a schematic representation of the documents that feed into and derive from clinical investigations; a brief description of these is provided in the glossary.

Types of clinical investigations

Before the release of ISO14155:2020,[8] the different types of clinical investigations were not clearly defined.[2] Annex I of this ISO guidance[8] covers this gap. It differentiates between **pre-market clinical investigations**, which are conducted with medical devices that have not yet gained market approval (CE-mark in Europe) and **post-market clinical investigations** (following market approval) as shown in Figure 2. For novel products in higher risk classes, first-in-human or feasibility studies may be necessary to gain initial information regarding the device's safety and to determine whether the procedure is feasible. These are comparable to phase II studies of medicinal products. Device or interventional modifications may be performed as necessary based on these studies, or new hypotheses will inform the design and sample size of pivotal clinical investigations, which are comparable to phase III trials of medicinal products. In the post-market phase, an investigation may be **interventional**, meaning an intervention occurs for the purpose of the investigation, e.g. additional x-ray assessments, or **non-interventional**, where the patients are treated according to the standard-of-care at the respective facility. **Company-sponsored** versus **investigator-initiated investigations**, and **prospective** investigations vs. **retrospective** analyses represent different approaches that are rather self-explanatory.

Trends in clinical investigation design

While clinical investigations were once fairly standard in the medical device field, there is a current trend towards new investigation designs, adapted from the ones used for medicinal products. Examples are **master protocols** that include a core protocol and sub protocols. Basket trials involve different patient populations, but the same product, and umbrella trials involve one patient population, but different products. The aim is to facilitate the creation of documents and their corresponding review by ethics committees and (if applicable) by competent authorities. Further details can be found in the article by Mackinnon and Gisbert.[14]

Another strategy is to combine different clinical investigation stages into one master protocol (e.g. pilot, pivotal and post market phase).

A novel, interesting, and efficient way of conducting randomised controlled trials is to "piggy-back" registries.[15] Furthermore, the concept of **adaptive trial design** is a strategy increasingly being used to make clinical investi-

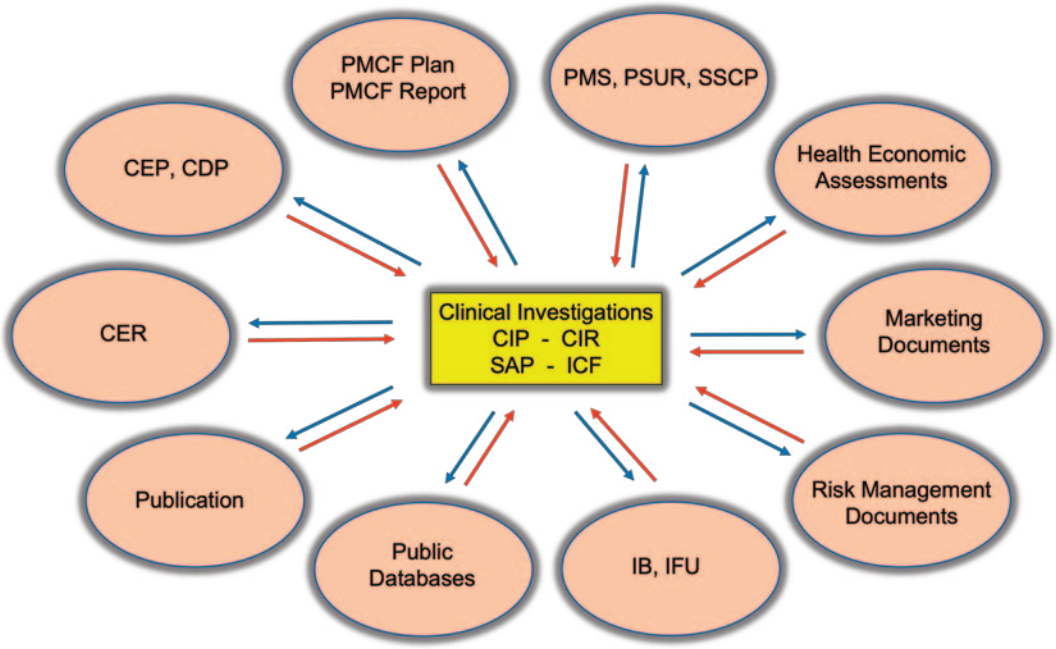


Figure 1. Documents associated with clinical investigations

Abbreviations: CDP, clinical development plan; CEP, clinical evaluation plan; CIP, clinical investigation plan; CIR, clinical investigation report; IB, investigator's brochure; ICF, informed consent form; IFU, instructions for use; PMCF, post-market clinical follow-up; PMS, post-market surveillance; PSUR, periodic safety update report; SAP, statistical analysis plan; SSCP, summary of safety and clinical performance

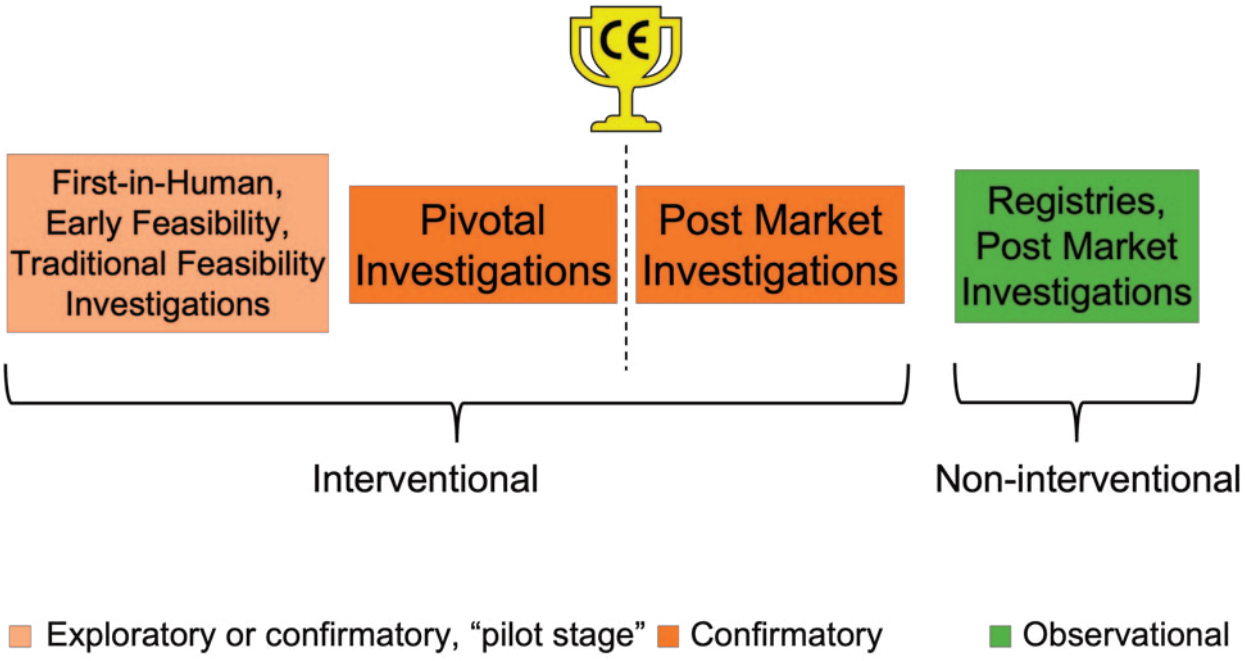


Figure 2. Clinical investigation types per ISO14155:2020[8]

gations more flexible and more efficient,[16] as well as **decentralised** trials.[17] New approaches are also being implemented for clinical investigation endpoints: While composite endpoints were routinely used in the past,[12] **hierarchical composite endpoints** are a new category defined by various disparate endpoints that are combined and are neither equivalent in severity nor assessed on the same scale.[18]

Lastly, and most importantly, as for medicinal products, **patient centricity** is becoming more important. The FDA released a statement to encourage patient engagement in medical device investigations and issued principles for Patient Reported Outcome Instruments for Use in medical device evaluations.[19,20]

EUDAMED

The European Database for Medical Devices (EUDAMED) is a multipurpose database created to address the need for greater transparency and traceability, as well as improved coordination of data related to medical devices that are marketed in the EU. It is composed of six modules, three of which are fully operational (Actor Registration, UDI Database and Registration of Devices, Certificates and Notified Bodies) and three of which are in various stages of readiness (Vigilance and Post-Market Surveillance, Clinical Investigation and Performance Studies [CIPS], and Market Surveillance).

The CIPS module will contain the key data from clinical investigations. Chapter 6, Article 73 of EU MDR 2017/745[3] stipulates that the user interface will be available in all official languages of the EU, and each clinical investigation will be assigned its own individual identification number. The sponsor will apply to conduct clinical investigations, follow up on them, report their results, and terminate them using this module. Serious adverse events and device deficiencies that arise during the course of the clinical investigation will be reported through the CIPS module. EU member states will be able to exchange certain sensitive information on clinical investigations that will be accessible only to EU member states and the Commission. Trial participants' personal information will not be accessible to the public.

Sponsors' confidential information, including the Investigator's Brochure and status of the device's conformity assessment, will not be accessible to the public unless there is an overriding public interest to disclose it. All other information, including the CIR, will be accessible to the public.

It is expected that all modules will be fully functional by Q2 2024. The first "Playground" launch date for the CIPS module was in mid-July 2022. The CIPS module is one of four whose use will become mandatory by the end of 2024, with the remaining two becoming mandatory by Q2 2026.[20] Notwithstanding, EUDAMED was originally scheduled to go live in May 2020, and delays have been announced three times thus far (Oct 2019, Oct 2021, and July 2022). Until EUDAMED is fully operational, MDCG 2021-1[9] provides guidance on alternative technical solutions.

> While clinical investigations were once fairly standard in the medical device field, there is a current trend towards new investigation designs.

Conclusion

In summary, medical device clinical investigations have similarities and differences compared to clinical trials of medicinal products. Medical writers with experience in pharmaceutical clinical studies should be able to switch to medical device clinical investigations easily, bearing in mind the above-mentioned peculiarities. With the growing sophistication of medical device clinical investigations and relatively greater potential for input by the medical writer, writing CIPs and CIRs could offer an attractive path on which to embark.

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Disclosures and conflicts of interest

None.

References

1. MEDDEV 2.7/1 revision June 4, 2016. Guidelines on Medical Devices [cited 2022 Nov 9]. Available from: https://www.medical-device-regulation.eu/wp-content/ uploads/ 2019/05/2_7_1_rev4_en.pdf
2. Döerr B, Whitman S, Walker S. Writing for medical devices compared to pharmaceuticals: an introduction. Med Writ. 2017;26:8–13.
3. EU MDR 2017/745. Regulation (EU) 2017/745 of the European Parliament and of the Council of April 5, 2017 on medical devices [cited 2022 Nov 9]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32017R0745
4. Miller FG, Kaptchuk TJ. Sham procedures and the ethics of clinical trials. J R Soc Med. 2004;97:576–8. doi:10.1258/jrsm.97.12.576.
5. Mallia R, Walter B. Differences between writing for medical devices and pharmaceuticals: An update. Med Writ. 2022;31:12–20.
6. Billiones R, Thomas KB. Medicinal products and medical devices in clinical trials conduct and disclosure. Med Writ. 2019;28:74–80.
7. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
8. ISO 14155:2020. Clinical investigation of medical devices for human subjects. Good clinical practice [cited 2022 Nov 9.] Available from: https://www.en-standard.eu/bs-en-iso-14155-2020-clinical-investigation-of-medical-devices-for-human-subjects-good-clinical-practice/
9. MDCG, Ongoing guidance development and deliverables of MDCG Subgroups [cited 2022 Nov 9]. Available from: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en
10. MEDDEV guidance documents [cited 2022 Nov 9]. Available from: https://www.medical-device-regulation.eu/meddev-guidance-list-download/
11. The Act on Medical Devices [cited 2022 Nov 9]. Available from https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Gesetze_und_Verordnungen/GuV/M/MPG_englisch.pdf
12. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the academic

Glossary

The table below is a non-exhaustive list of documents that relate to clinical investigations. Further details are provided in the regulations and guidelines as specified in the section *Applicable Regulations*. Please note that not all documents are required for all medical devices, e.g. the Periodic Safety Update Report is only required for class IIa, IIb, and III devices, and the Summary of Safety and Clinical Performance only for class III and implantable devices.

Clinical Development Plan (CDP)	The CDP describes the clinical strategy of a device and is part of the Clinical Evaluation Plan (CEP). Clinical Investigations (CI) shall be conducted according to the CDP, but information obtained from the CI may also feed back to the CDP.
Clinical Evaluation Plan (CEP)	The clinical evaluation assesses clinical data of a device to verify its clinical safety and performance. The CEP plans the clinical evaluation and contains the CDP. Information obtained from the CI may feed back to the CEP (e.g. outcomes, areas that require further investigations).
Clinical Evaluation Report (CER)	The CER reports the outcomes of the clinical evaluation. CIs are an integral part of the CER, and Clinical Investigation Reports (CIR) are often attached to the CER. The CER may also feed into the CI, e.g. if gaps are identified that need to be covered through a CI.
Health Economic Assessment	Data from the CI may feed into the Health Economic Assessment. These might e.g. be Quality of Life questionnaires, length of hospital stay, operation time, etc. This is particularly relevant for novel devices for which reimbursement needs to be established.
Investigator's Brochure (IB)	The Investigator's Brochure summarises all preclinical and clinical data of a device. It is required for CIs with investigational devices. For CIs with an approved device, the Instructions For Use (IFU) usually suffices.
Instructions for Use (IFU)	The IFU is the packaging leaflet that describes how to use the device, how to store it, the potential complications associated with the device, etc. The IFU is required for CIs, but information obtained in CIs may also feed into the IFU, e.g. if new complications associated with the device have been identified.
Marketing documents	Marketing documents refer to communications to the public. This may be via websites, marketing brochures, etc. All clinical claims raised in these materials need to be substantiated with clinical data.
Post-Market Clinical Follow-Up (PMCF) plan	The PMCF plan specifies the collection and evaluation of clinical data. Even after a medical device gains market access (CE-mark in Europe), the manufacturer is frequently obliged to perform additional PMCF studies, e.g. with long-term follow-up, or to investigate the device in a larger group of patients to confirm the safety and performance of the device, or to register rare side-effects. The PMCF plan includes not only CIs, but also the screening of literature, etc. CIs shall be conducted according to the PMCF plan, but outcomes from CIs may also feed into the PMCF plan.
PMCF report	Amongst other PMCF activities, the PMCF report summarises the outcomes of PMCF CIs.
Post Market Surveillance plan (PMS)	Outcomes of CIs may feed into the post market surveillance plan and report (e.g. incidents).
Periodic Safety Update Report (PSUR)	The PSUR summarises the outcomes of the PMCF, but also contains data derived from other sources (e.g. complaint data).
Publication	The results of every CI should be published in a peer-reviewed journal. At least the outcomes must be made publicly accessible.
Entries in public databases	CIs need to be registered in public databases (for registries, it is recommended but not required). CIs will be registered in EUDAMED once the database is operational. Until then, the most commonly used database for trial registration is ClinicalTrials.gov.These databases may also contain the outcomes of CIs.
Summary of Safety and Clinical Performance (SSCP)	The SSCP provides an update on the safety and performance of the device and summarises clinical data. It shall be made available to the public (via EUDAMED once the database is live). Identified gaps may feed into the design of new CIs.
Risk management documents	Risk management documents feed into several other documents (e.g. the IFU) that have to be considered when writing a CIP, particularly in terms of risks, precautions, and warnings. Outcomes of CIs may likewise feed into risk management (e.g. event rates, new risks, new precautions).

research consortium-2 consensus document. Circulation. 2018;137: 2635–50. doi:10.1161/CIRCULATIONAHA.117.029289
13. Norberg J. A beginner´s guide to writing clinical investigation plans and reports for medical devices. Med Writ. 2022;31:34–9.
14. Mackinnon J, Gisbert A. Master protocol studies: Embracing the "new normal". Med Writ. 2021;30:83–9.
15. Infinity-Swedehart Registry Based Randomized Clinical Trial (R-RCT) [cited 2022 Nov 9]. Available from: https://clinicaltrials.gov/ct2/show/NCT04562805
16. Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: Why use them, and how to run and report them. BMC medicine. 2018;16:1–5. doi:10.1186/s12916-018-1017-7
17. Mackinnon J. Bringing decentralised clinical trial protocols to life. Med Writ. 2023;32(1):12–8. doi:10.56012/rtqr5570
18. Hahn RT, Ben-Yehuda O, Leon MB. Endpoints for tricuspid regurgitation trans-catheter therapy trials. Prog Cardiovas Dis. 2019;62:479–81. doi:10.1016/j.pcad.2019.11.019.
19. Statement on FDA efforts to encourage patient engagement in medical device clinical investigations [cited 2022 Nov 9]. Available from: https://www.fda.gov/news-events/press-announcements/statement-fda-efforts-encourage-patient-engagement-medical-device-clinical-investigations
20. Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation: Guidance for Industry and Food and Drug Administration Staff, And Other Stakeholders [cited 2022 Nov 9]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-selecting-developing-modifying-and-adapting-patient-reported-outcome-instruments-use
21. EUDAMED Time line. The European Commission planning – June 2022 [cited 2022 Nov 9]. Available from: https://health.ec.europa.eu/system/files/2022-07/md_eudamed_timeline_en.pdf

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Joan D'souza completed a bachelor's in homeopathic medicine and surgery, a post-baccalaureate program in clinical research, and then pursued a Juris Doctorate in law (J.D.). She has worked for various hospitals, clinical research organisations, and pharmaceutical companies. She now works as a freelance regulatory writer and a pharmacovigilance consultant. Joan is an active member of EMWA Medical Devices and Pharmacovigilance Special Interest Groups.

Trial Trivia Answers *from page 53*

1. What is the earliest documentation of a trial?

No, it wasn't James Lind. Allegedly, the Bible documented the first human experimentation in the Book of Daniel 1:12-15. "*Test your servants for ten days; let us be given vegetables to eat and water to drink. Then let our appearance and the appearance of the youths who eat the king's food (meat and wine) be observed by you, and deal with your servants according to what you see.*"

It was an interventional, open-label, active-controlled, parallel-group comparative study. The outcome is summarised by Arun Bhatt in his paper entitled Evolution of Clinical Research: A History Before and Beyond James Lind. The paper also describes the origins of the use of placebo and the double-blind study design.[1] Definitely a delight for history buffs!

But what about my hero James Lind? He was the Scottish doctor who researched the treatment of scurvy among British sailors. The documentation in his book *A Treatise of the Scurvy* earned him the title of "Father of Clinical Trials".[1–2] Because of his research, vitamin C became part of our daily diet and the British got nicknamed "limey" as limes and other types of citrus fruits became staple on British naval ships.

2. What is the largest pre-approval trial in terms of the number of participants to date? The smallest?

The largest trial is supposedly the **Rotavirus Efficacy and Safety Trial (REST)** registered under NCT00090233.[3] It enrolled a whopping 69,274 infants aged 6 to 12 weeks. The COVID-19 trials also ranked among the top ten, with at least 30,000 participants.[4]

Generally, vaccine trials require a large number of participants. At the other end of the spectrum, trials in orphan drugs understandably have low numbers of participants, sometimes fewer than 15.[5] Having worked in both Vaccinology and Rare Disease areas, I am privileged to have been involved in projects at these two extremes. Most trials fall somewhere in between.

3. What is the most expensive trial?

I can't find a straight answer. A survey of 138 pivotal trials used as basis for approval of 59 new therapeutic agents by the FDA from 2015 to 2016 showed median estimated cost of $19.0 million (range < $5 million to $346.8 million).[5] However, more recent reports actually place the median cost at $648 million for new cancer drugs.[6]

4. What is the longest-running clinical trial?

This website[7] lists the 10 longest-running clinical trials, with the study on **Botulinum Toxin for Involuntary Movement Disorders** as the record holder. Clinicaltrials.gov records show that this trial (NCT00001208) supposedly started in 1989 and is still recruiting to date.[8] This means this trial even predates EMWA.

References

1. Bhatt A. Evolution of clinical research: a history before and beyond James Lind. Perspect Clin Res. 2010 Jan;1(1):6–10.
2. Nellhaus E, Davies T. Evolution of clinical trials throughout history. Marshall J Med. 2017 3(1). doi:10.18590/mjm.2017.vol3.iss1.9
3. Brown A. It's official: COVID-19 vaccine trials rank among the largest. 2020 Nov 20 [cited 2023 Jan22]. Available at https://www.evaluate.com/vantage/articles/news/snippets/its-official-covid-19-vaccine-trials-rank-among-largest
4. Rotavirus Efficacy and Safety Trial (REST)(V260-006) [cited 2023 Jan 22]. Available at https://clinicaltrials.gov/ ct2/show/NCT00090233?term=NCT00090233&draw=2&rank=1
5. Moore TJ, Zhang H, Anderson G, et L. Estimated costs of pivotal trials for novel therapeutic agents approved by the US Food and Drug Administration, 2015-2016. JAMA Intern Med. 2018;178(11):1451–1457. doi:10.1001/jamainternmed.2018.3931
6. Bahrenburg C. FDA pivotal trial costs vary by more than $300 million. 2018 Sep 24 [cited 2023 Jan 22]. Available at https://www.hcplive.com/view/fda-pivotal-trial-costs-vary-by-more-than-300-million
7. The longest running clinical trials [cited 2023 Jan 22]. Available at https://www.pharmaceutical-technology. com/most-read/length-of-clinical-trials/
8. Botulinum toxin for the treatment of involuntary movement disorders [cited 2023 Jan 22]. Available at: https://clinicaltrials.gov/ct2/show/NCT00001208?term=Botulinum+Toxin+for+involuntary+movement+disorders&draw=2&rank=1

Clinical trials in the Eurasian Economic Union

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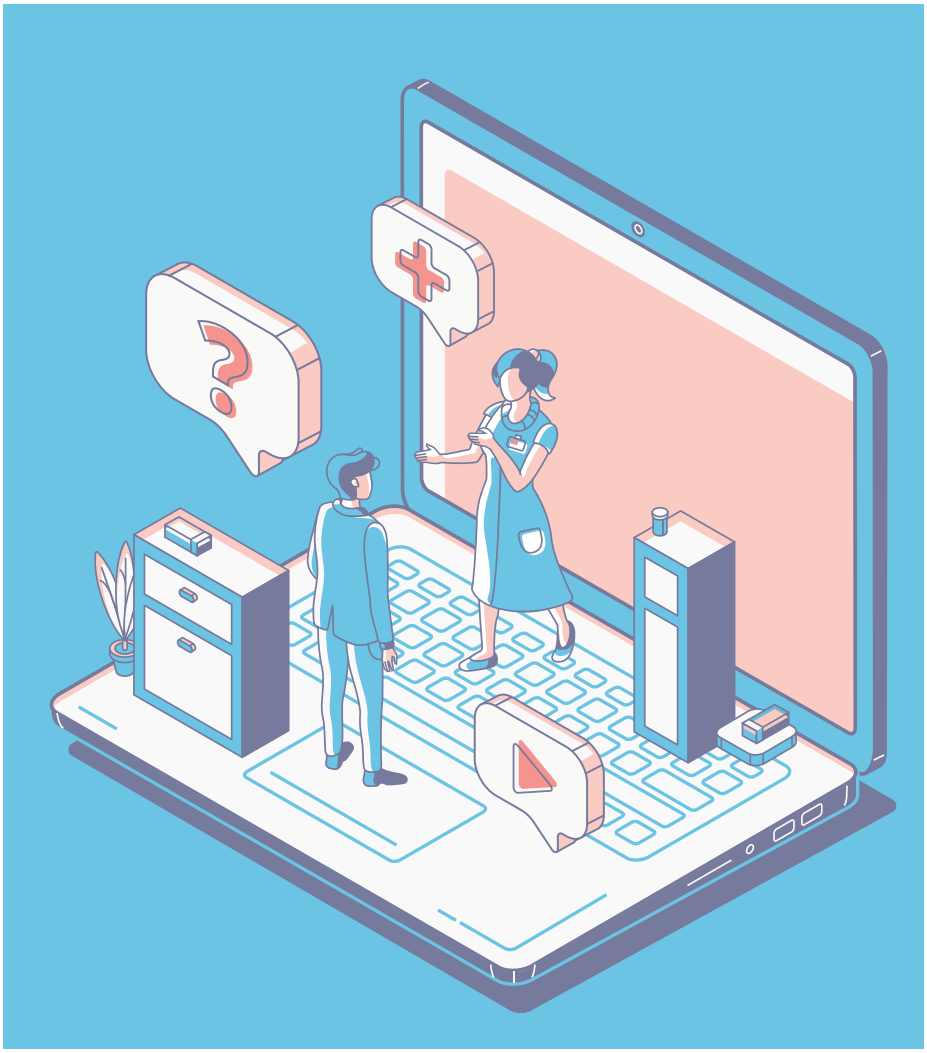
Abstract
In January 2021, the single market of medicines of the Eurasian Economic Union (EAEU) was launched. This article describes the current status of the transition to unified rules for the registration of medicinal products and the main regulatory documents for conducting clinical trials in the EAEU region.



The Eurasian Economic Union (EAEU) is an international organisation for regional economic integration, which includes the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, the Kyrgyz Republic, and the Russian Federation. With a total population of 183.6 million,[1] the EAEU provides free movement of goods, services, capital, and labour, and pursues coordinated, harmonised, and unified policy in the sectors determined by its treaty and international agreements within the Union.[2]

In December 2014, the EAEU countries signed the Agreement on Common Principles and Rules of Circulation of Medicinal Products Within the EAEU, which aimed to provide access to the unified market for medicines, regulating the safety, efficacy, and quality by current scientific standards.

The main document that details the procedures for the transition to a single drug market is the Rules for Registration and Expertise of Medicinal Products for Medical Use, issued in December 2016. According to this document, starting January 1, 2021, the registration of medicines in EAEU countries must be carried out in accordance with the unified requirements of the Union. This provision also changed the scope of clinical trials for such drugs. Now, clinical trials must be planned and conducted according to EAEU procedures. For drugs that have already been registered in EAEU countries, a transitional period has been contemplated until December 31, 2025, within which companies must bring the registration dossiers of drugs in line with EAEU legislation. (It is important to note that the dossier structure is now fully compliant with the Common Technical Document standard).

If existing clinical data are considered insufficient, new clinical trials, designed in accordance with EAEU requirements, should be conducted.

If existing clinical data are considered insufficient, new clinical trials, designed in accordance with EAEU requirements, should be conducted.

The single unified market for medicines has been actively developing in recent years. A specialised platform named "Common market of medicines",[3] available in six languages including English, contains complete and accurate information about the authorised drugs. It also contains results of pharmacological inspections and state supervision of the turnover of medicines, both conducted by authorised bodies of the member

states of the EAEU, as well as other information about the circulation of medicines.

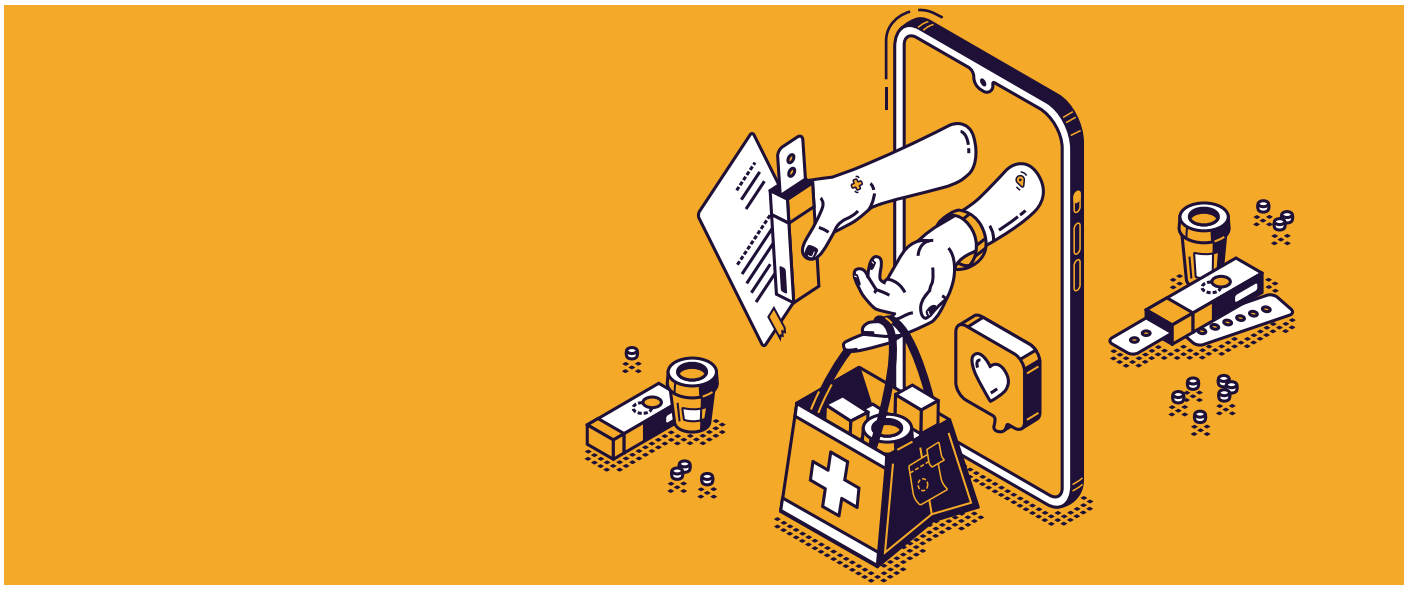
All regulatory documents are published in the EAEU legal portal.[4] The main documents governing the planning and conduct of clinical trials are summarised in Table 1. Importantly, documents related to clinical trials are thoroughly harmonised with the requirements of International Council on Harmonisation (ICH), FDA, and EMA, making it convenient for all parties, including those outside the EAEU.

Clinical trials should be conducted in accordance with the EAEU Good Clinical Practice (GCP), which is harmonised with the ICH E6 (R1) guideline. However, it is worth noting that the EAEU GCP guideline (named Rules of Good Clinical Practice of the Eurasian Economic Union) has a different document structure and includes several stand-alone regulatory parts: a GCP guideline, requirements for the structure and content of the clinical study report (harmonised with the ICH E3 guideline), a list of essential protocol amendments, the procedure for submitting safety information during the study, and requirements for the writing of the safety update report.

Within the EAEU agenda, there are also plans to create various information resources regarding data on the circulation of medicines. More specifically, the Unified Register of Medicines of

Table 1. The Eurasian Economic Union regulatory guidelines

The Eurasian Economic Union (EAEU); http://www.eaeunion.org/
EAEU legal portal; https://docs.eaeunion.org/
Eurasian Economic Commission Council Resolution No. 78 of November 03, 2016 **Rules of marketing authorization and assessment of medicinal products for human use** (updates available)
Eurasian Economic Commission Council Resolution No. 79 of November 03, 2016 **Rules of Good Clinical Practice of the Eurasian Economic Union**
Eurasian Economic Commission Council Resolution No. 85 of November 03, 2016 **Rules for conducting bioequivalence studies of medical products within the framework of the Eurasian Economic Union** (updates available)
Eurasian Economic Commission Council Resolution No. 87 of November 03, 2016 **Rules of pharmacovigilance practice (GVP) of the Eurasian Economic Union** (updates available)
Eurasian Economic Commission Council Resolution No. 89 of November 03, 2016 **Rules for research of biological medicinal products of the Eurasian Economic Union** (updates available)
Decision of the Board of the Eurasian Economic Commission No. 202 of November 26, 2019 **Guidelines for preclinical safety studies for the purpose of conducting clinical trials and drug registration**
Recommendation of the Board of the Eurasian Economic Commission No. 11 of July 17, 2018 **Guidelines on general considerations for clinical trials**
Recommendation of the Board of the Eurasian Economic Commission No. 8 of March 12, 2019 **Guidelines for the selection of the dose of drug**
Recommendation of the Board of the Eurasian Economic Commission No. 25 of September 2, 2019 **Guidelines for the preclinical and clinical development of drug combinations**
Recommendation of the Board of the Eurasian Economic Commission No. 42 of December 17, 2019 **Guidelines for the selection of non-investigational drugs for clinical trials**
Recommendation of the Board of the Eurasian Economic Commission No. 15 of September 15, 2020 **Guidelines for quality assessment and bioequivalence studies of certain groups of drugs**
Recommendation of the Board of the Eurasian Economic Commission No. 19 of November 03, 2020 **Guidelines on the principles of biostatistics in clinical trials of medicinal products**



the EAEU has been created, which contains information on all drugs that have been registered or re-registered in accordance with the rules of the Union. Unfortunately, there is no unified register of clinical trials yet. This information is still only available on the national platforms of each respective EAEU member state.

On the one hand, the transition to the requirements of the EAEU allowed all participants in the drug market of the EAEU countries to speak the same language and provided uniform approaches to clinical trials and registration of drugs that comply with international standards. On the other hand, the procedure appeared to be quite stressful for the industry. For instance, new processes have to be planned and implemented from scratch, and there are gaps in the EAEU regulations for clinical trials and drug registration. Additionally, the existing guidelines are constantly updated, making it challenging to follow all the latest updates and regulatory news, which is compounded by the lack of an established procedure for scientific advice to obtain timely clarifications from the regulator.

Unfortunately, there is no unified register of clinical trials yet.

At the same time, it is hard to ignore the importance of the very fact of the establishment of a single market for the circulation of drugs in the EAEU and all the effort the working groups of the EAEU put into the formation of regulatory requirements that meet international standards. For experts involved in the planning and conducting of clinical trials that involve medical writing, the introduction of universal requirements for the structure and content of documents and clinical trial design has greatly simplified their working routine and facilitated communication between experts from EAEU countries and pharma companies that plan to bring drugs to the EAEU market.

All stakeholders count on the resolution of existing issues, which will ultimately ensure the circulation of high-quality, safe, and effective drugs in the unified EAEU market.

Disclosures and conflicts of interest

The authors declare no conflict of interest.

References

1. About EAEU [cited 2022 Nov 30]. Available from: http://www.eaeunion.org/presentation/?lang=en#about.
2. The Eurasian Economic Union (EAEU) [cited 2022 Nov 28]. Available from: http://www.eaeunion.org/.
3. Common market of medicines [cited 2022 Nov 28]. Available from: https://portal.eaeunion.org/en-us/_layouts/15/cit.eec.impop/portal.landings/drugs.aspx.
4. EAEU Legal portal [cited 2022 Nov 28]. Available from https://docs.eaeunion.org/en-us.

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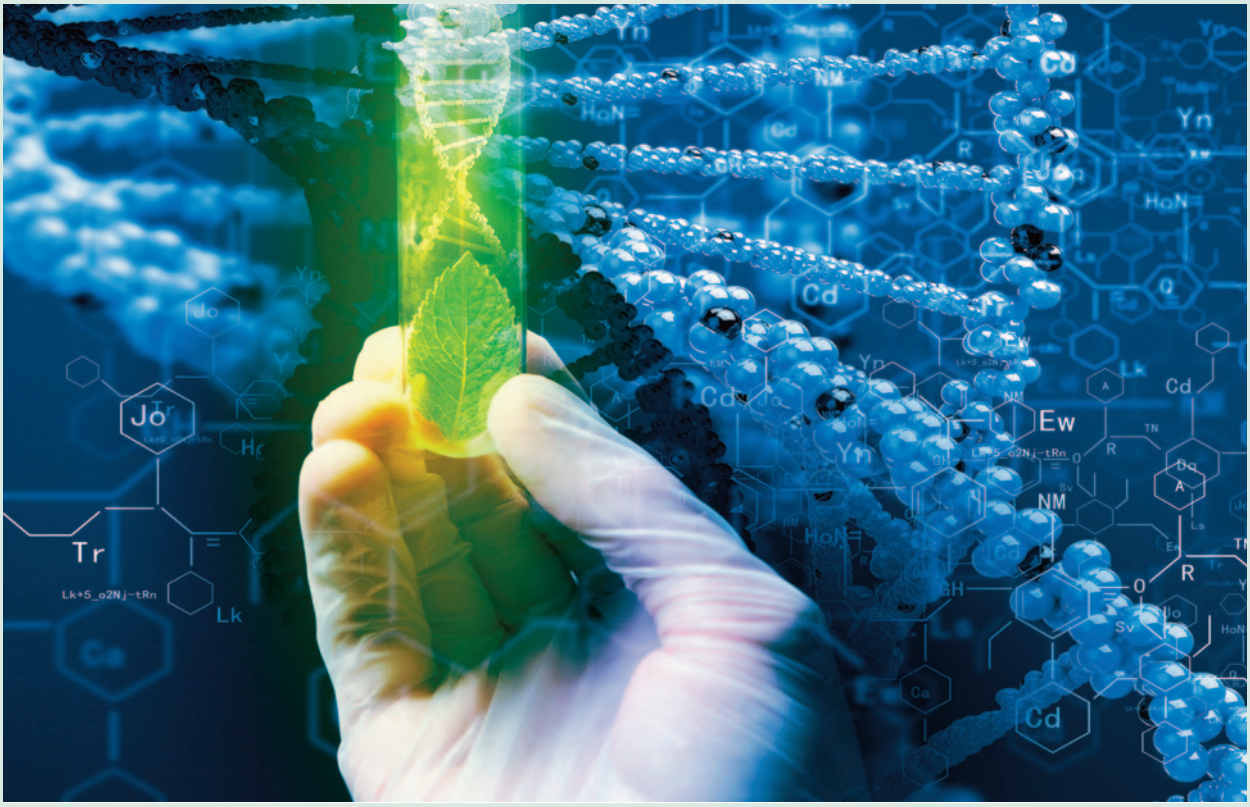
Don't miss!

The December 2023 edition



Biotechnology

Biotechnology uses biological systems and living organisms in R&D and production processes. Biotechnologies include biologic and biosimilar pharmaceuticals like monoclonal antibodies, vaccines and advanced therapy medicinal products, for example, gene and cell therapies and tissue engineered products. In addition, biotechnologies support the product lifecycle, for instance, in non-clinical work using in silico, in vitro, and animal testing methods. Also, support services personnel like those in biobanks and supply chains require an understanding of biotechnology. This issue focuses on the crucial role of writing and communications in biotechnology and product development.

Guest editor: Jennifer Bell
The deadline for feature articles is September 1, 2023.

Clinical study reports:
A snapshot for aspiring medical writers

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Abstract
Clinical study reports (CSR) are detailed documents that provide a comprehensive and transparent account of the conduct and results of a clinical trial. They are an important source of information for the regulatory authorities, healthcare professionals, and the public, and are used to assess the safety and efficacy of medical treatments. This article presents an overview of the steps involved in writing and submitting CSRs to regulatory authorities, as well as reporting clinical trial findings to the scientific community and the public.

The clinical study report (CSR) is a document that describes the results of a clinical trial and is used to assess the safety and effectiveness of a new medical treatment.[1-3] CSRs provide detailed information about the design, conduct, and results of clinical studies. A CSR is prepared by the sponsor of the clinical trial to report study outcomes to regulatory authorities, such as the FDA in the US or the EMA in the EU. Regulatory authorities use the information in the CSR to evaluate the safety, efficacy, and quality of the medicinal product and to determine whether it should be approved for marketing. Information provided in the CSR is also used by researchers and other stakeholders including patients and the public to evaluate the safety and efficacy of the treatment being tested and to make decisions about its potential use in clinical practice.

Types of CSRs

Different types of CSRs can be prepared depending on the specific context and purpose of the clinical trial, as well as the requirements of the regulatory authority reviewing the data.

Examples include:

- **Full CSR:** The most comprehensive type of CSR. It includes all the data and analyses from the clinical trial. Full CSRs are typically used for regulatory purposes, such as submitting data to the FDA in support of a new drug application.
- **Interim CSR:** Used to report on the progress of a clinical trial that is still ongoing. Interim CSRs are typically shorter than full CSRs, are written once the primary and secondary endpoints are met and may be used for marketing authorisation application (MAA) before the clinical trial is complete. Data on the exploratory endpoints and long-term follow-up are included later in the full CSR.
- **Abbreviated CSR:**[4,5] Used for studies that do not contribute to the evaluation of efficacy or provide definitive information on the clinical pharmacology of the investigational product. Abbreviated CSRs contain abbreviated method and efficacy sections, as well as a detailed safety section.
- **Synoptic CSR:**[4] Generally prepared for studies that are not relevant in evaluating the effectiveness and clinical pharmacology of the

medicinal product but provide data for evaluating its safety (e.g. studies evaluating routes of drug administration for which marketing approval is not required, incomplete studies enrolling fewer than one-third of intended participants, and early general phase 1 safety-tolerance studies).

Structure of a CSR

The content and format of a CSR are based on The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guideline E3 on the Structure and Content of Clinical Study Reports (ICH E3),[3] which was approved in 1996. The detailed structure of a CSR may vary slightly depending on the specific requirements of the regulatory authority to which it is being submitted. Medical writers use the ICH E3 template,[3] the TransCelerate template,[6] and the CORE (Clarity and Openness in Reporting: E3-based) Reference to create CSRs that are compliant with regulatory guidelines.[7–10]

A CSR typically includes the following components:

- **Synopsis:** A brief overview of the main findings and conclusions of the study
- **Introduction:** Background information about the medicinal product being studied, including its intended use and the rationale for the study
- **Methods:** The study design, objectives and endpoints, patient population, interventions, and outcomes; includes information about the ethical considerations and any statistical analyses that were performed
- **Results:** The findings of the study, including both numerical data and descriptive information; also includes tables, figures, and other visual aids to illustrate the results
- **Discussion:** The clinical implications of the study findings and limitations of the study
- **Conclusion:** The main findings and conclusions of the study
- **Appendices:** Additional information or materials that are relevant to the study such as protocols, informed consent forms, data tables, figures and listings, as well as patient narratives

The detailed structure of a CSR may vary slightly depending on the specific requirements of the regulatory authority to which it is being submitted.

Submission of a CSR

The submission process for CSRs differs depending on the regulatory authority. Under the Clinical Trials Regulation (EU) No 536/2014 (EU CTR), EU member states and European Economic Area (EEA) countries have, since January 31, 2022, been able to use the Clinical Trial Information System (CTIS) to submit all clinical trial data.[11–13] The CTIS harmonises the submission, assessment, and supervision processes for clinical trials; A single application can be submitted through the CTIS for review by all EU/EEA countries. The CTIS also facilitates interactions between clinical trial sponsors and the regulatory authorities in EU/EEA countries throughout the clinical trial, and replaced the EU Drug Regulating Authorities Clinical Trials Database (EudraCT) on January 31, 2023.[14,15] The CTIS will store all documents related to clinical trials (e.g. CSRs and clinical study protocols) and will also serve as a publicly accessible database for clinical trial data. However, the CTIS does not accept or evaluate MAAs for the commercialisation of medicinal products, which must be made separately.

As per Article 37 of the EU CTR, sponsors who have had their MAAs approved are required to submit a full CSR to the CTIS within 30 days after the marketing authorisation approval.[9,16] Article 37(4) also requires the sponsor to submit a summary of the clinical trial results to the CTIS, irrespective of the outcome of the clinical trial, within one year from the end of the trial in adults (6 months for a clinical trial in the paediatric population), in all the EU languages in which the study was conducted.[9,17] Sponsors are required to provide a summary of results and a lay summary after the end of each clinical trial in the EU. The CSR, summary of clinical trial

Table 1. Training courses on writing clinical study reports

Course name	Organisation	Description
Regulatory Medical Writing Bundle[40]	Regulatory Affairs Professionals Society	Introduces medical writing, different types of regulatory applications, and techniques for improving document quality
Regulatory Medical Writing Training Programme[41]	Groep Biomedische Wetenschappen KU Leuven	Provides an overview of clinical development and a practical introduction to writing clinical and regulatory documents
Regulatory Affairs Training Program[42]	Duke University School of Medicine	Provides an overview of premarket regulatory work related to drugs, biologics, and medical devices
Regulatory Writing[43]	University of California San Diego Extended Studies	Provides training on writing CSRs, information on regulations, and guidance governing regulatory documents in the US and the EU
Regulatory Writing[44]	The University of Chicago	Focuses on the basics of editing regulatory documents, as well as collaborating on creating biomedical regulatory packets and navigating the writing, submission, and auditing processes
CRED Regulatory Document Writing and Management[45]	The Organization for Professionals in Regulatory Affairs	Focuses on the theory and practice of writing effective regulatory documents and communications
Writing Clinical Study Reports[46]	European Center for Clinical Research Training	Covers the principles of clinical research writing and reporting, including how to write a CSR. The course includes interactive exercises and case studies
Clinical Study Reports: Mastering the Essential Skills[47]	European Medical Writers Association	Double workshop for medical writers with little or no experience in writing CSRs. Workshops on the CORE Reference as well as variations of CSRs are also available

Abbreviations: CSR, clinical study report

results, and the lay summary are disclosed publicly. In the US, a full CSR is submitted as part of a New Drug Application (NDA) to the FDA.[18] Unlike in the EU, CSRs in the US are not disclosed publicly.

Sponsors in the EU are required to submit all CSRs that are intended to be used for marketing authorisations.[19,20] As part of an MAA, CSRs are compiled in Module 5 of the common technical document (CTD), a standardised format for submitting regulatory information to health authorities globally.[21,22] The CTD consists of five modules that cover different aspects of the submission (e.g. quality, safety, and efficacy of the product), and includes a comprehensive overview of the clinical trials and their results.

The CSR, summary of clinical trial results, and the lay summary are disclosed publicly in the CTIS.

Reporting findings published in CSRs

Findings reported in CSRs are disseminated in several ways.

- **European Public Assessment Reports:**[23] Reports prepared by the EMA and published on the EMA website. These reports provide information on the medicinal product, including the evaluation process and the decision to approve or reject the MAA
- **Clinical trial registries:** The EudraCT or CTIS databases of the EMA, the International Clinical Trials Registry Platform of the WHO,[24] and the ClinicalTrials.gov registry[25] in the US
- **Other public disclosure platforms:** EMA clinical data website under EMA Policy 0070,[26] Health Canada Public Release of Clinical Information[27]
- **Lay language summaries:** Published in the CTIS or on company websites
- **Publications:** Manuscripts in peer-reviewed journals, conference posters and presentations, abstracts, preprints, and plain-language summaries. Good Publication Practice guidelines[28–30] mandate that all biomedical research should be published in peer-reviewed journals in a timely manner and that reporting of biomedical research should follow all applicable laws and guidelines. Several checklists exist to ensure that findings from a CSR are reported accurately and transparently in peer-reviewed medical journals.[31] Examples include:
  - **CONSORT (Consolidated Standards of Reporting Trials):**[32] A guideline for reporting randomised, controlled trials
  - **STROBE (STrengthening the Reporting of OBservational studies in Epidemiology):**[33] A guideline for reporting observational studies
- **Product information:** Clinical trial results are also reported in the summary of product characteristics or prescribing information (a document prepared for healthcare professionals), as well as package leaflets (aimed at the patient).

Writing your first CSR

Medical writers specialising in regulatory documents typically spend a lot of time writing CSRs. A medical writer working on a CSR needs to have sound knowledge of how clinical trials are planned, conducted, and reported.[34–39] For an aspiring medical writer, there are several online training programs and courses on how to write a CSR (Table 1). Writing a CSR is a team effort involving multiple stakeholders including clinicians, biostatisticians, regulatory specialists, safety experts, and the clinical study management team. Therefore, the medical writer also needs strong communication and project management skills. Planning timelines and determining stakeholder roles before the start of the project can help with effective project management. CSR templates based on the ICH E3 guideline, TransCelerate template, and CORE Reference can help the medical writer create a document that meets rigorous regulatory standards.

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Disclosures and conflicts of interest

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References

1. American Medical Writers Association. What Is a clinical study report? A medical communicator's guide [cited 2022 Dec 19]. Available from: https://blog. amwa.org/what-is-a-clinical-study-report-a-medical-communicators-guide.
2. EMA. ICH E6 (R2) Good clinical practice – Scientific guideline [cited 2022 Dec 19]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf.
3. EMA. ICH Topic E 3. Structure and content of clinical study reports 1996 [cited 2022 Dec 19]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-structure-content-clinical-study-reports-step-5_en.pdf.
4. FDA. Guidance for industry submission of abbreviated reports and synopses in support of marketing applications 1999 [cited 2023 Jan 19]. Available from: https://www.fda.gov/files/drugs/published/Submission-of-Abbreviated-Reports-and-Synopses-in-Support-of-Marketing-Applications..pdf.
5. Alfaro V, Cullell-Young M, Tanovic A. Abbreviated clinical study reports with investigational medicinal products for human use: Current guidelines and recommendations. Croat Med J. 2007;48(6):871–7. doi: 10.3325/cmj.2007.6.871.
6. Hamilton S, Bernstein AB, Blakey G, 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. Res Integr Peer Rev. 2019;4:16. doi:10.1186/s41073-019-0075-5
7. CORE Reference. Clarity and openness in reporting: E3-based [cited 2022 Dec 19]. Available from: https://www.core-reference.org/.
8. EMWA. The CORE Reference project [cited 2022 Dec 19]. Available from: https://www.emwa.org/resources/core-reference/.
9. Hamilton S, Bernstein AB, Blakey G, et al. Developing the Clarity and Openness in Reporting: E3-based (CORE) Reference user manual for creation of clinical study reports in the era of clinical trial transparency. Res Integr Peer Rev. 2016;1:4. doi:10.1186/s41073-016-0009-4
10. Hamilton S, D J. CORE Reference – a tool for modern clinical study reports in an era of increasing transparency and disclosure. Medical Writing. 2018;27(2):64–7.
11. EMA. Clinical Trials Information System (CTIS) [cited 2022 Dec 19]. Available from: https://euclinicaltrials.eu/.
12. EMA. Clinical Study Reports submission [cited 2022 Dec 19. Available from: https://www.ema.europa.eu/en/documents/other/quick-guide-clinical-study-reports-submission-ctis-training-programme-module-13_en.pdf.
13. EMA. Clinical Trials Regulation [cited 2022 Dec 19]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation#clinical-trials-information-system-section.
14. EMA. EudraCT. [cited 2022 Dec 19]. Available from: https://eudract.ema.europa.eu/.
15. EMA. Key Information for Sponsors on CTIS [cited 2022 Dec 19]. Available from: https://www.ema.europa.eu/en/documents/other/clinical-trials-information-system-key-information-sponsors-ctis_en.pdf.
16. European Commission. Clinical trials – Regulation EU No 536/2014 [cited 2022 Dec 19]. Available from: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en#eu-clinical-trial-portal-and-database.
17. Barnes A, Patrick S. Lay summaries of clinical study results: An overview. Pharmaceut Med. 2019;33(4):261-8. doi:10.1007/s40290-019-00285-0
18. US FDA. New Drug Application (NDA) [cited 2022 Dec 19]. Available from: https://www.fda.gov/drugs/types-

applications/new-drug-application-nda.
19. EMA. Marketing authorisation [cited 2022 Dec 19]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation.
20. EMA. Obtaining an EU marketing authorisation, step-by-step [cited 2022 Dec 19]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step.
21. EMA. ICH M4 Common technical document (CTD) for the registration of pharmaceuticals for human use - organisation of CTD - Scientific guideline [cited 2022 Dec 19]. Available from: https://www.ema.europa.eu/en/ich-m4-common-technical-document-ctd-registration-pharmaceuticals-human-use-organisation-ctd#documents-section.
22. ICH harmonisation for better health. M4:The Common Technical Document [cited 2022 Dec 19]. Available from: https://www.ich.org/page/ctd.
23. EMA. European public assessment reports: Background and context [cited 2022 Dec 19]. Available from: https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context.
24. WHO. International Clinical Trials Registry Platform (ICTRP) [cited 2022 19 Dec]. Available from: https://www.who.int/clinical-trials-registry-platform.
25. US National Library of Medicine. ClinicalTrials.gov [cited 2022 Dec 19]. Available from: https://www.clinicaltrials.gov/.
26. EMA. Clinical data publication [cited 2023 Jan 19]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication.
27. Health Canada. Guidance document on Public Release of Clinical Information: Profile page [cited 2023 Jan 19]. Available from: https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/profile-public-release-clinical-information-guidance.html.
28. Battisti WP, Wager E, Baltzer L, et al. Good publication practice for communicating company sponsored medical research: GPP3. Ann Intern Med. 2015;163(6): 461–4. doi:10.7326/m15-0288
29. DeTora LM, Toroser D, Sykes A, et al. Good publication practice (GPP) guidelines for company-sponsored biomedical research: 2022 update. Ann Intern Med. 2022;175(9):1298-304. doi:10.7326/m22-1460
30. ISMPP. Introducing GPP 2022 [cited 2022 Dec 19]. Available from: https://www.pathlms.com/ismpp.
31. Equator Network. Enhancing the QUAlity and Transparency Of health Research [cited 2022 Dec 19]. Available from: https://www.equator-network.org/.
32. CONSORT. Consolidated Standards of Reporting Trials [cited 2022 Dec 19]. Available from: https://www.consort-statement.org/.
33. STROBE. Strengthening the reporting of observational studies in epidemiology [cited 2022 Dec 19]. Available from: https://www.strobe-statement.org/.
34. Friedman LM, CD F. Fundamentals of Clinical Trials. 4th ed2010.
35. LF W. Targeted Regulatory Writing Techniques: Clinical Documents for Drugs and Biologics2009.
36. RAPS. Fundamentals of US Regulatory Affairs. 11th ed.
37. RAPS. Regulatory Writing: An Overview. 2nd ed.
38. RAPS. Fundamentals of EU Regulatory Affairs. 9th ed.
39. RAPS. Key Regulatory Topics: eCTD.
40. Regulatory Affairs Professionals Society. Regulatory Medical Writing Bundle [Complete Package] [cited 2022 Dec 19]. Available from: https://www.raps.org/products/regulatory-medical-writing-bundle-complete-package.
41. Groep Biomedische Wetenschappen KU Leuven. Regulatory Medical Writing Training Programme [cited 2022 Dec 19]. Available from: https://gbiomed.kuleuven.be/english/phd/PhD_Researchers/Skills/medical-writing-training-programme.
42. Duke University School of Medicine. Regulatory Affairs Training Program [cited 2022 Dec 19]. Available from: https://medschool.duke.edu/research/research-support/research-support-offices/office-regulatory-affairs-and-quality-3.
43. UC San Diego Extended Studies. Capstone: Regulatory Writing [cited 2022 Dec 19]. Available from: https://extendedstudies.ucsd.edu/courses-and-programs/capstone-regulatory-writing.
44. The University of Chicago. Regulatory Writing [cited 2022 Dec 19]. Available from: https://professional.uchicago.edu/find-your-fit/non-credit-certificates/regulatory-writing.
45. TOPRA. CRED Regulatory Document Writing and Management [cited 2022 Dec 19]. Available from: https://www.topra.org/TOPRA/TOPRA_Member/Events/Event_Display.aspx?EventKey=DOC22O.
46. European Center for Clinical Research Training. Writing Clinical Study Reports [cited 2022 Dec 19]. Available from: https://eccrt.com/writing-clinical-study-reports/.
47. EMWA. Clinical study reports –Mastering the essential skills (double workshop) [cited 2023 Jan 19]. Available from: http://filemaker.emwa.org/workshops/view_workshop.php?recid=1318

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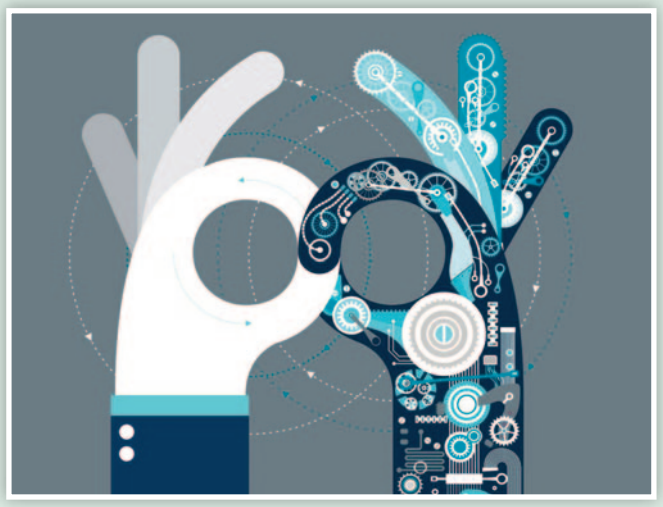

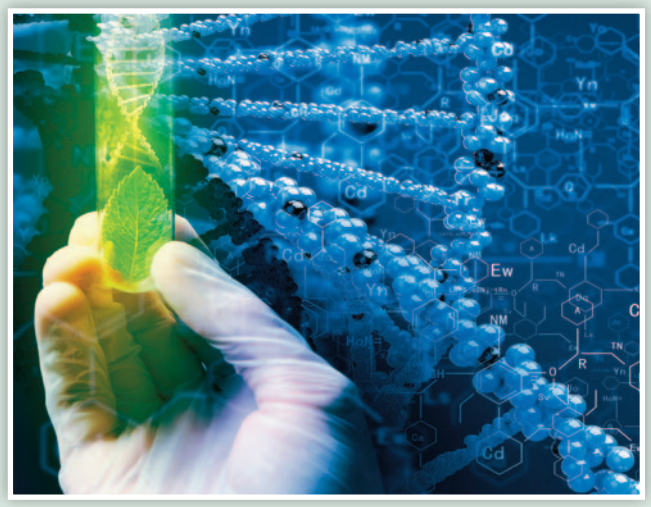

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Overview of the European General Data Protection Regulation (GDPR) impact on medical writing for clinical trials

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Abstract

The European General Data Protection Regulation 2016/ 679 (GDPR) aims to ensure the security and privacy of individuals in the European Union (EU). Companies located within and outside of the EU must comply with GDPR when processing personal data of EU citizens.

Medical writing includes the development of documents related to clinical research. To develop those documents, medical writers have access to personal data, including health information considered as sensitive data. Therefore, medical writing falls within the purview of GDPR and must comply with its requirements.

This article is an overview of the impact of GDPR on medical writing including security measures such as anonymisation, pseudonymisation, and data minimisation techniques. It also provides an overview of the technical and organisational actions in the framework of medical writing to guarantee respect of data subjects' rights and freedoms.

Introduction to the GDPR

The European General Data Protection Regulation 2016/ 679 (GDPR) became effective in May 2018 and aims to harmonise data protection laws across EU member states.[1] The goal of GDPR is to render individuals control over their personal data, and to enhance security measures, including information technology (IT) for data protection. GDPR defines personal data as *"any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person"* (Art. 4 GDPR).

Medical writing under the purview of GDPR

In the framework of clinical research, special categories of personal data are processed including demographics (e.g. age, gender, ethnicity, race), health data, and genetic data, some of which are considered as sensitive data and require more security safeguards (Art. 32 GDPR).[1,2]

Institutions performing clinical trials often engage service providers for medical writing activities. Since medical writers handle personal data, they are considered as data processors and have responsibilities and obligations listed in GDPR Art. 28 *("Where processing is to be carried out on behalf of a controller, the controller shall use only processors providing sufficient guarantees to implement appropriate technical and organisational measures in such a manner that processing will meet the requirements of this Regulation and ensure the protection of the rights of the data subject")*.[1] However, medical writing service providers are often overlooked as data processors, thus lacking the control and implementation of appropriate security measures to protect personal data. Consequently, the risks for data breaches and harm to an individual's freedoms and rights that might occur in the medical writing framework are underestimated.

It is important to distinguish between medical writing of scientific publications (including articles in scientific journals, abstracts, and presentations for congresses) and medical writing in a clinical study (including case reports, safety reports). Depending on the type of document to be written, writers have access to different types of data in terms of directly identifiable personal data, anonymised or pseudonymised (Table 1).

Article 4 (5) of GDPR defines pseudonymisation as *"the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person"*.[1]

Recital 26 of GDPR defines anonymised data as *"information which does not relate to an identified or identifiable natural person or to personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable"*.[1]

Consequently, GDPR compliance requirements may differ for different medical writing tasks.

Publications writing

In case of most scientific publications (e.g. systematic reviews and meta-analysis) where writers use aggregated data and group statistics, the risk of re-identification of individuals is almost null as the data may be considered as anonymised and do not fall under the scope of GDPR. However, a thorough analysis of anonymisation techniques must be done to ensure that the data are truly anonymous.

The EU Data Protection Working Party, an independent European advisory body on data protection and privacy, issued under Article 29 of Directive 95/46/EC an opinion regarding anonymisation techniques.[3] The European Medicine Agency (EMA) issued guidance for anonymisation techniques specifically for the publication of clinical data.[7] For personal data to be considered truly anonymous, three cumulative criteria must be fulfilled (Figure 1).

1. No individualisation or singling out: The identification of an individual must be rendered impossible by any means, neither direct, nor by isolation of some information from datasets or combination of datasets.
2. No correlation or linkability: The correlation of records to an individual or to a group of individuals within a cohort is impossible.

Table 1. Documents developed by medical writers that involve handling personal data of study subjects and requiring GDPR compliance

Documents	Study subject's personal data
Clinical Study Report	Typically, pseudonymous data, but combination of datasets can single out the individual. Exceptionally, directly identifiable data when sending to authorities.
Statistical outputs	Typically, pooled data, pseudonymous data.
Safety reports	Identifiable data, directly identifiable data might occur exceptionally.
Case reports	Identifiable data, directly identifiable data might occur exceptionally.
Articles for scientific journals	Typically, pseudonymous data, but combination of datasets can single out the individual.

Still, the linkability stays valid in this case.

3. No inference: Personal data cannot be inferred to an individual, meaning that the probability to deduce a value of an attribute within values of a set of attributes is very low. However, to achieve full anonymisation in practice is almost impossible, as shown by regenerative models that the success of re-identification in incomplete datasets is high.[4,5] Therefore, caution should be taken when evaluating whether personal data is truly anonymised.

Writing for clinical trials

Patient data in clinical trials are not truly anonymous. To ensure individuals' privacy during a clinical trial as per Good Clinical Practice (GCP), when a subject is enrolled in a clinical trial, a code (e.g. Subject ID) is attributed to replace the name and surname. Hence the individual cannot be directly identified. This procedure is called pseudonymisation. Importantly, pseudonymised personal data fall under the scope of GDPR.[1]

> When medical writers have access to the directly or indirectly identifiable personal data of study subjects, they fall under the purview of GDPR.

Pseudonymisation procedures commonly used in the framework of medical writing are data generalisation, data transformation, encryption, and hashing (see example in Table 2). However, these techniques are not completely immune to re-identification attacks.

For personal data to be effectively pseudonymised, four cumulative criteria should be met (Figure 2).[3]

- Firstly, no individualisation is possible, yet by using additional information (e.g. key to the code), the individual can be singled out.
- Secondly, the key to the code must be kept confidentially by the data exporter (that might have the role of data controller or data processor), and typically at the investigational sites of a clinical trial.
- Thirdly, appropriate safeguards must be put in place to avoid data breaches and render to the exporter control over the personal data.
- Lastly, a thorough analysis must be performed to ensure that it is impossible to single out the individual even in case of cross-reference, considering the availability of such data.

Thus, when publishing results in scientific journals, it is necessary to remove or replace certain elements that might lead to identification of the individual.[6,7] Some examples of techniques are:

- Perform double coding of patient code that was initially attributed by the investigational site
- Banding: Replace subjects' ages with age ranges (reasonably calculated)
- Relativity: Replace calendar dates with relative dates, i.e in relation to study milestones such as inclusion, randomisation... (e.g."visit 1", "visit 2")[7]
- Generalisation or randomisation:
  - Date of birth replaced by year of birth or derived age
  - Avoid mentioning the country and/ or city of the investigational site. Site information elevated to larger geographic area
  - Avoid mentioning the name or the alphabetical code of the investigational site

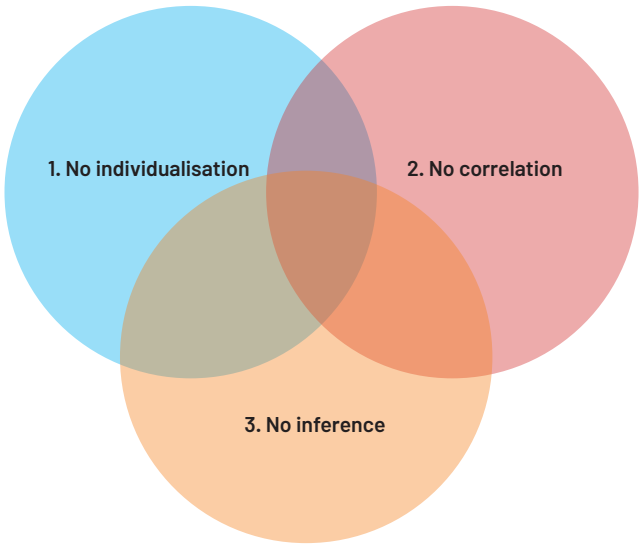

Figure 1. Three cumulative criteria to consider personal data truly anonymised

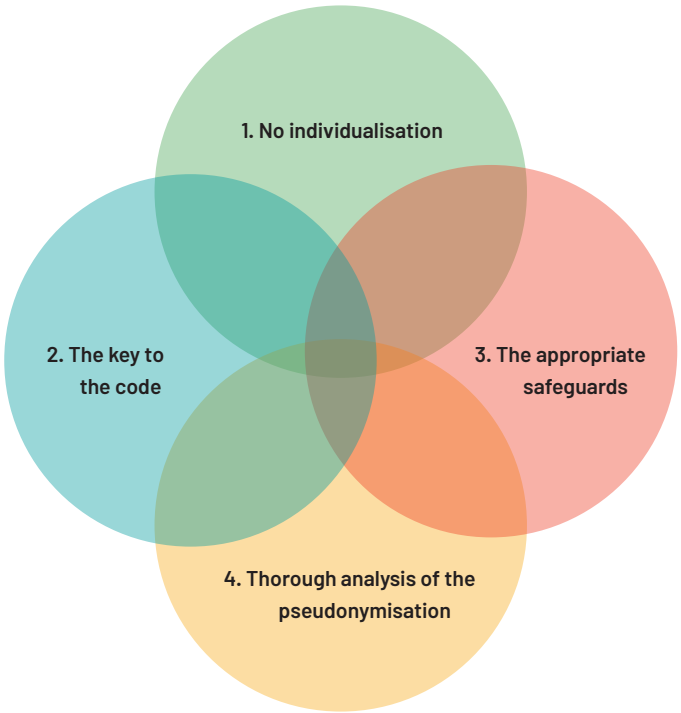

Figure 2. Four cumulative criteria to consider personal data effectively pseudonymised

Table 2. Example of data masking

Name, address, date of birth	Patient's code	Period of treatment	Body Mass Index
	RM54LM286	< 2 years	16
	XD96CV749	> 2 years	18
	SZD95LE206	< 2.5 years	20
	...	...	...

- Rare adverse events: preferred term elevated to body system
- Remove or aggregate outliers: e.g. subjects >89 years removed, low frequency groups aggregated

Sharing a minimum amount of personal data to support the scientific findings is in line with the GDPR principle of data minimisation (Article 5 (c)).

An exception is the publication of individual patient data such as case reports about rare diseases, diagnostic challenges, and treatments of uncommon situations. To ensure patient's privacy, it is compulsory to remove any unnecessary detail and images that can lead to re-identification of the individual.[8,9]

When medical writers have access to the identifiable personal data of study subjects, they fall under the purview of GDPR. Access to identifiable data often occurs during writing of the documentation for real-world evidence. One of the data source examples is Council of International Organizations for Medical Science

Table 3. Checklist of some technical, organisational, and IT controls that might help prevent unwanted modifications, loss, or destruction of data, as well as decrease the likelihood and the severity of risks triggered in case of data breaches

Organisational controls

- ☐ Set-up data protection policy.
- ☐ Set-up data breach procedure describing step-by-step action to be taken to contain the breach.
- ☐ Set-up archiving and data destruction procedure.
- ☐ Make the personnel aware about the policies and procedures related to data protection.
- ☐ Use confidentiality clauses in contracts with processors and freelancers who handle personal data.
- ☐ Raise privacy culture.

Logical security controls

- ☐ Ensure control and restriction of the access to the sources containing personal data.
- ☐ Limit the number of users who may have access to personal data.
- ☐ Limit time access to personal data.
- ☐ Use robust passwords, secure internet connections, data encryption, installing malicious software on workstations.
- ☐ Set-up clear procedures that state how, to whom, by whom, and under what circumstances personal data can be accessed, erased, or sent back to the sponsor.
- ☐ Set-up procedures that define traceability methods to track the loggings to the documents containing personal data.
- ☐ Encrypt the data.

Physical security controls

- ☐ Ensure physical security of servers and platforms of data exchange.
- ☐ Ensure physical security of workstations.
- ☐ Set-up procedure how to manage paper format containing personal data.
- ☐ Set-up policies describing how physical maintenance of hardware is managed.
- ☐ Set-up procedures describing actions to take against on-human source of risk.

(CIOMS) forms to report suspect adverse reactions. These forms are completed by the health care professional in free text, hence lacking data protection safeguards.

Also, identifiable data might be accessible, during the writing of a Clinical Study Report (CSR), case reports, safety reports, as well as other documentations for regulatory submissions (Table 1). To draft safety reports, medical writers might use sources such as clinical and safety databases, patient registries, but also patient-generated data through mobile devices, apps, patient-reported outcomes (e.g. eDiaries) and electronic health reports. Moreover, the information contained in the study reports should match with the clinical trial data. This step involves quality control check-up by additional members of the medical writing team and statisticians and increases the risk for data security.

Medical writers are considered as data processors and play an important role in data protection.

Conclusions

To summarise, it is important to set-up a clear methodology of data pseudonymisation, anonymisation, and data minimisation to ensure the privacy of subjects participating in the clinical trials. Technical, organisational, and IT safeguards must be adopted by the medical writing service providers (Table 3). Writers must respect the data minimisation principle of GDPR by providing only the minimum data necessary to meet the objective of the scientific or regulatory document being written.

In conclusion, GDPR states that data controllers and processors must put in place security measures and ensure privacy by design and by default. However, the regulation does not provide clear instructions as to what those measures are and how they should be implemented. Medical writers are considered to be data processors and play an important role in data protection. Each organisation that provides medical writing services should adopt the necessary measures according to its budget and size in order to comply with data protection regulations. Medical writers as freelancers are also subject to the above-mentioned requirements. With the new EU Clinical Trials Regulation 536/2014, more and more emphasis is set on public disclosure of documents which increases this need for security. An infallible system does not exist, and data breaches occur daily. Therefore, it is important to propagate privacy culture and raise data protection

awareness within the medical writers' community to ensure that subject's rights and freedoms are not compromised.

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References

1. 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). Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016R0679
2. European Data Protection Board (EDPB) Guidelines 3/2018 on the territorial scope of the GDPR. Available from: https://edpb.europa.eu/sites/default/files/files/file1/edpb_guidelines_3_2018_territorial_scope_after_public_consultation_en_1.pdf
3. Article 29 Data Protection Working Party, Opinion on anonymization techniques, Adopted on 10 April 2014. Available from: https://ec.europa.eu/justice/article-29/documentation/opinion-recommendation/files/2014/wp216_en. pdf
4. Bentzen HB, Castro R, Fears R, et al. Remove obstacles to sharing health data with researchers outside of the European Union. Nat Med. 2021;27(8):1329–33. doi:10.1038/s41591-021-01460-0
5. Rocher L, Hendrickx JM, de Montjoye YA. Estimating the success of re-identifications in incomplete datasets using generative models. Nat Commun. 2019;10(1):3069. doi:10.1038/s41467-019-10933-3do
6. CNIL's referenced methodology MR-001, Research in health sector with consent. Available from: https://www.cnil.fr/fr/declaration/mr-001-recherches-dans-le-domaine-de-la-sante-avec-recueil-du-consentement
7. EMA Policy 0070. External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use, ver 1.4. 15 Oct 2018. Available from: 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
8. The Case Reports (CARE) guidelines [cited 2022 Nov 27]. Available from: https://www.care-statement.org
9. Roguljić M, Ščepanović R, Rees M. Writing case reports, consent for publication and General Data Protection Regulation (GDPR). Case Rep Womens Health. 2020;27:e00204. doi:10.1016/j.crwh.2020.e00204

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Connecting the dots across the writing continuum

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Abstract

A medical writer has a unique opportunity to be involved with documents across the various stages of a product's lifecycle. At the start of their careers, writers typically specialise in documents that are created in a particular phase of drug development and are accordingly titled as early phase writers, late phase writers, publication writers, and so on. As writers progress in their careers, depending on each writer's interests, they could be exposed to a plethora of documents across the writing continuum (starting from pre-clinical to post-approval phases of drug development). Writers thus have the potential to play an important role in ensuring data is disseminated to various stakeholders in a coherent and seamless manner throughout the product's lifecycle. Let's take a look at the various aspects to keep in mind as writers move from one document to the next and help connect the dots!

Be informed of the different document types

Some common documents that medical writers are associated with include protocol and amendments, investigator's brochures (IB), clinical study reports (CSRs), clinical summaries and overviews, integrated summaries, result summaries, lay summaries, and manuscripts. There are various other documents that medical writers undertake (both pre- and post-approval of a drug) but let's limit ourselves to the common ones (Figure 1).

It is important as a first step for a writer to understand how these various documents fit into the product lifecycle. A good resource to start with would be the common technical document (CTD) to get a sense how various clinical documents are structured. The specifications of the CTD are followed by pharmaceutical companies for most regulatory submissions. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline M4 provides relevant details regarding the structure of CTD.[1] Similarly, looking at post-approval regulatory requirements of various countries can give a writer an idea of associated post-approval documents. Writers are usually exposed to one document at a time, and the focus is so much on the document itself, that sometimes the big picture is not provided or is not clear. Here, a little proactiveness from the writer to understand the overall product lifecycle and the requirement of different documents at specific timeframes within this lifecycle, would go a long way in ensuring the writing itself becomes clearer and more robust.

Nuances of each document: Be well-versed with document templates

Most pharmaceutical companies and contract research organisations maintain document-specific templates based on formats recommended by various guidelines and regulations. These templates can be obtained at the ICH website for clinical documents such as ICH E3 for CSR, ICH E6 for IB, ICH E6, and M11 for protocol.[2] For the EU specific documents, like EMA content and format for non-interventional post-authorisation safety studies, can be found on the EMA website.[3] Furthermore, the EQUATOR Network is a good source for various reporting guidelines and checklists.[4] Following the formats and recommendations provided by regulators would increase the chances of a successful submission.

Thus, writers should familiarise themselves with the document and template, reading all instructions carefully before starting to work on any assigned document. Not following document guidelines and instructions could potentially lead to unsuccessful submissions or delayed approval decisions. Special care is also needed when you are working on amendments or updates, where the tendency is to take a previous version of the document and work on it. Not checking for template updates made during the interim could result in the amendment not reflecting important changes. Additionally, it is important for writers to familiarise and follow the guidelines of not just the document they are working on, but also other templates in the continuum, especially as they take on senior roles within the team.

Prepare each document while keeping the next in mind

As mentioned previously, one way for writers to familiarise themselves with each document in the writing continuum is by having a look at the document templates (see previous section) and also looking at the structure of the written documents. Writers can learn from the teams that work with these templates or find it online. Most

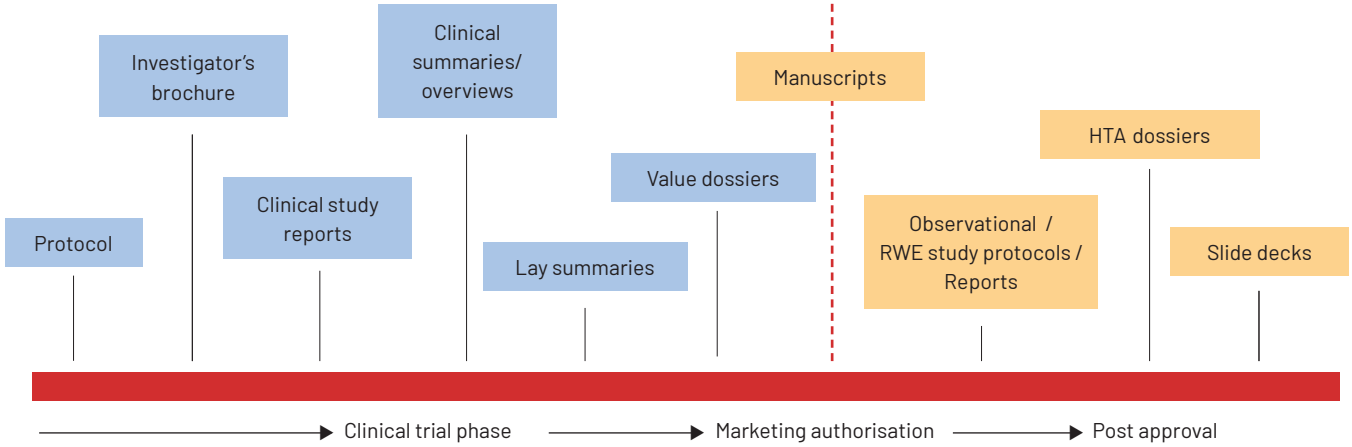

Figure 1. Example document types across the writing continuum

Abbreviations: HTA, health technology assessment; RWE, real world evidence

Abbreviations appearing in this article

CSR, clinical study report;
CTD, common technical document;
CTIS, Clinical Trial Information System;
EU, European Union;
FDA, Food and Drug Administration;
HTA, health technology assessment;
IB, investigator's brochure;
ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use;
PSUR, periodic safety update report;
RWE, real world evidence

Understanding the connections among documents saves the writer time.

of the templates are publicly available on the EMA website. As writers get familiar with various documents, they will soon learn, or ought to learn, that data from one document usually flows into one or more downstream documents – sections from the protocol are used in the shell of the CSR, results from the CSR go into multiple documents like summaries, IBs, manuscripts, and others. Understanding the connections among documents saves the writer time by ensuring all necessary data are captured in the document, thus making it available to be incorporated in subsequent documents. To achieve this, writers would have to efficiently collaborate with other departments, and also other writers, to get all the required data for their document. Ultimately, having a document with all necessary data would further help downstream document writers adhere to timelines and aid in timely submissions.

Have the same writer author multiple documents of a study

In companies that have a large writing team, writers could be assigned to work on a specific study document and then moved to another study or project depending on team requirements. As an example, multiple studies may be ongoing in parallel and there may be a need for additional writers to work on an important submission dossier. In this case, the writer who worked on a study protocol will later have to work on a high priority project, and some *other* writer may be assigned to work on the CSR for the previous study. Even though sometimes challenging, if possible, try to forecast and plan resources ahead of time and have the same writer available to work on most documents related to a single study. This would ensure better continuity in the flow of data and writing styles from one document to the next.

Ensure all documents are telling the same story – consistently

It may not always be possible for the same writer to work on all the documents, especially for outsourced writing work. In such a scenario, it becomes especially important for the lead writer who is ultimately managing the submission package to ensure that all documents are telling the same story. For example, make sure that results presented in the CSR are also reflected in the IB, summaries, and manuscript. For consistency across documents, all stakeholders need to be kept informed of updates or changes, ensuring uniform messaging in all the documents and writers play a crucial role here!

Be aware of guidelines and requirements

It is always helpful for writers to be aware of the latest guidelines and requirements. For instance, medical writers should be aware that clinical trials should be registered in a public trial registry before or at the first patient recruitment as a consideration for publication by journals following International Committee of Medical Journal Editors recommendations.[5] Similarly, some countries have the requirement to publish clinical trial results on specific registries. For example, for a clinical trial conducted in the US, trial results must be published in clinicaltrials.gov.[6] On the other hand, there is no FDA regulation for lay summaries of trial results, but in the EU, lay summaries are a regulatory requirement.[7]

> Real world studies enable researchers and healthcare providers go beyond data collected in clinical trials that can be limiting by the characteristics of the sample population selected for the trial.

Knowing applicable regulatory requirements and guidelines at the get-go would help writers prepare documents accordingly, and would require minimal efforts later on for other subsequent activities, like removing any patient identifiers or personal details from clinical documents such as CSRs. This way minimal redaction is required when the CSR needs to be made publicly available. Most document templates have these instructions, and writers should read

them carefully before starting to write. And if they are not sure why certain things are being requested in the template, that is their cue to ask or read up on relevant requirements.

Beyond clinical documentation

The writing continuum doesn't stop after product approval, and a whole bunch of documents are written post-approval. These documents are written for real world/post-approval studies (protocols, reports, manuscripts/posters). Post-approval, periodic safety reports are required and label updates may be needed. It happens frequently that a certain adverse event not observed in clinical trials occurs in the real world setting after the drug is approved. Based on the relevant evidence gathered, the pharmaceutical company is obligated to inform the regulators and, in some cases, update the drug's label accordingly.

Marketing authorisation holders gather safety evidence for marketed products from various sources and share that information at regular intervals with the regulatory authorities through periodic safety update reports (PSURs). In the EU, once a product is marketed, PSURs must be submitted every six months after initial placement on the EU market for two years, then once a year for the next two years, and thereafter at three-year intervals.[8] Additionally, regulatory authorities have defined guidelines on what data should be reported on an expedited basis. In most countries this rapid transmission is usually focused on the expedited reporting of adverse reactions that are both serious and unexpected.

It is important to understand that R&D, safety monitoring, improvements in drug effectiveness, and innovation needs to continue beyond drug approval, and the information needed to support these comes from post-approval studies. Real world studies enable researchers and healthcare providers to go beyond data collected in clinical trials that can be limiting by the characteristics of the sample population selected for the trial. Evidence from real-world studies provide valuable information on how the drug performs in the real world, especially in terms of long-term safety and effectiveness, economic performance, and comparative effectiveness with other treatments.[9] More recently, with many regions and payers requiring value of the drug to be demonstrated prior to deciding on pricing/ reimbursements/ insurance, pharma companies need to have robust value dossiers. And writers are increasingly becoming an integral part of teams working on various such value dossiers – global value dossier, local value dossier, health technology assessment (HTA) reports, academy of managed care pharmacy dossier, and many others. Apart from economic data, there are a lot of clinical and literature data that go into these documents as evidence. Writers are required to weave all the information at hand – starting from established evidence from clinical studies to pooled analysis, literature evidence, real world data, economic data, etc. into a document that brings out the true value of a drug – thus playing an active role at this end of the continuum, too!

Conclusions

We get a sense of the wide variety of documents writers could be handling at various phases of a product's lifecycle, and a writer's role in ensuring data from one document connects to the next. Well written and structured submission dossiers would aid in speeding up the approval process and similarly in the post-approval stages would help in disseminating the right value of the product to a large audience including regulators, patients, healthcare providers, payers/insurers, and others, thus showcasing the pivotal role that writers play throughout the product lifecycle.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by her employer or EMWA.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. ICH M4: The Common Technical Document [cited 2023 Jan 29]. Available from https://www.ich.org/page/ctd
2. ICH Guidelines [cited 2023 Jan 29]. Available from https://www.ich.org/page/ich-guidelines
3. EMA: Human Regulatory – Post-authorisation safety studies (PASS) [cited 2023 Jan 29]. Available from https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass-0
4. Equator Network – Enhancing the QUAlity and Transparency Of health Research [cited 2023 Jan 29]. Available from https://www.equator-network.org/
5. International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals [cited 2022 Nov 17]. Available from: https://www.icmje.org/recommendations/
6. FDA Amendments Act (FDAAA) Section 801 and the Final Rule [cited 2022 Nov 17]. Available from: https://clinicaltrials.gov/ct2/manage-recs/fdaaa#WhichTrialsMustHaveResults
7. Barnes A, Patrick S. Lay summaries of clinical study results: An overview. Parmaceut Med. 2019;33(4):261-8. doi:10.1007/s40290-019-00285-0
8. EMA Guideline on good pharmacovigilance practices (GVP), Module VII – Periodic safety update report (Rev 1) [cited 2023 Jan 29]. Available from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf
9. Blonde L, Khunti K, Harris SB, et al. Interpretation and impact of real-world clinical data for the practicing clinician. Adv Ther. 2018;35(11):1763–74. doi:10.1007/s12325-018-0805-y

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News from the EMA

The articles included in this section are a selection from the European Medicines Agency (EMA)'s News and Press Releases archive. More information can be found on the Agency's website: www.ema.europa.eu.

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Photo: Erik Karits

New vaccine to protect people in the EU and worldwide against dengue

October 14, 2022

European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for Dengue Tetravalent Vaccine (live, attenuated) developed by Takeda GmbH, used to prevent disease caused by dengue virus serotypes 1, 2, 3 and 4 in people from four years of age.

Dengue is a mosquito-borne tropical disease caused by four types of the dengue virus, leading to mild, flu-like symptoms in most people. However, a small number of patients develop severe disease, with potentially fatal bleeding and organ damage. The risk of severe disease is higher in people who have been infected a second time.

According to the World Health Organization, there are approximately 390 million dengue infections per year worldwide, with an estimated death rate of 20,000 to 25,000 per year, primarily in children. Before 1970, only nine countries had experienced severe dengue epidemics, while today the disease is endemic in more than 100 countries, including in Europe. It is the second most-diagnosed cause of fever after malaria among travellers returning from low- and middle-income countries.

This is the first time the CHMP simultaneously reviews a medicinal product meant for the European Union (EU) market, under the centralised procedure, and non-EU countries, under the "EU-Medicines for all" programme – or EU-M4all. EMA's initiative to support parallel applications for the EU-M4all opinion and the centralised procedure aims to make innovative or generic medicines and vaccines that address unmet medical needs or are of major public health interest available in Europe and globally faster, while avoiding duplication of efforts from regulators.

An antiviral therapy for dengue virus infection is not available, and most of the current measures that rely on mosquito control are not very efficient in preventing disease. There is an already approved vaccine, but the dengue tetravalent vaccine shows a wider protection for young children and people older than 45 years old. In light of this, a global unmet public health need is being addressed.

The benefits and safety of the current vaccine have been evaluated in 19 clinical trials that enrolled more than 27,000 people aged between 15 months and 60 years, from both endemic and non-endemic regions. The results of the studies show that dengue tetravalent vaccine prevents fever, severe disease, and hospitalisation caused by any of the four serotypes of the dengue virus.

The most frequently reported suspected adverse events after any dose of this vaccine were injection site pain, headaches, muscle pain, and feeling generally unwell.

Medicines submitted under the EU-M4all programme are assessed by the CHMP in collaboration with the WHO and the target countries, combining EMA's scientific review capabilities with the epidemiology and local disease expertise of WHO and experts and national regulators in the target countries. The CHMP scientific opinion under the EU-M4All procedure supports global regulatory capacity building and contributes to the protection and promotion of public health beyond the EU by assessing medicines for countries where regulatory capacity may be limited. National regulators can rely on the CHMP's scientific assessment to decide on the use of the medicine in their countries.

First therapy to treat transplant patients with post-transplant lymphoproliferative disease

October 14, 2022

The EMA has recommended a marketing authorisation in the EU for Ebvallo (tabelecleucel), developed by Atara Biotherapeutics Ireland Limited, for the treatment of adult and paediatric patients who experience a serious complication following solid organ transplantation (SOT) or bone marrow transplantation (hematopoietic cell transplant – HCT) called EBV+ PTLD. This is one of the most important malignancies after transplantation. It is a result of the immunosuppression caused by the medication required to reduce the possibility of rejection of the transplanted organ or cells and the most common form of this condition is associated with the Epstein-Barr virus. Ebvallo is indicated in patients after a transplant and who have received at least one prior therapy when the symptoms of the disease come back after treatment (relapsed) or when the treatment does not work (refractory).

A significant unmet need exists for patients who fail first-line therapies as they have only weeks to a few months' survival after treatment failure, and other treatment options are limited. The aim of new treatments is to achieve the disappearance of all signs of cancer after treatment (complete remission) and prolong overall-survival, thereby reducing transplantation-related mortality of patients with EBV+ PTLD.

Tabelecleucel, the active substance of Ebvallo, targets and eliminates infected cells. It is an advanced therapy medicinal product made of cells of the immune system called T-cells that have been taken from a donor (allogeneic). The T-cells are first mixed with another type of white blood cells in the immune system (B-cells) from the same donor that have been infected with the Epstein-Barr virus so that the T-cells learn to recognise infected B-cells. The T-cells are then grown to increase their numbers. When the medicine is given to the patient, the T-cells are expected to attack and kill the patient's own infected B-cells, thereby helping to control cancers associated with the virus.

Ebvallo was supported through EMA's PRIority MEdicines (PRIME) scheme, which provides early and enhanced scientific and regulatory support to medicines that have a particular potential to address patients' unmet medical needs.

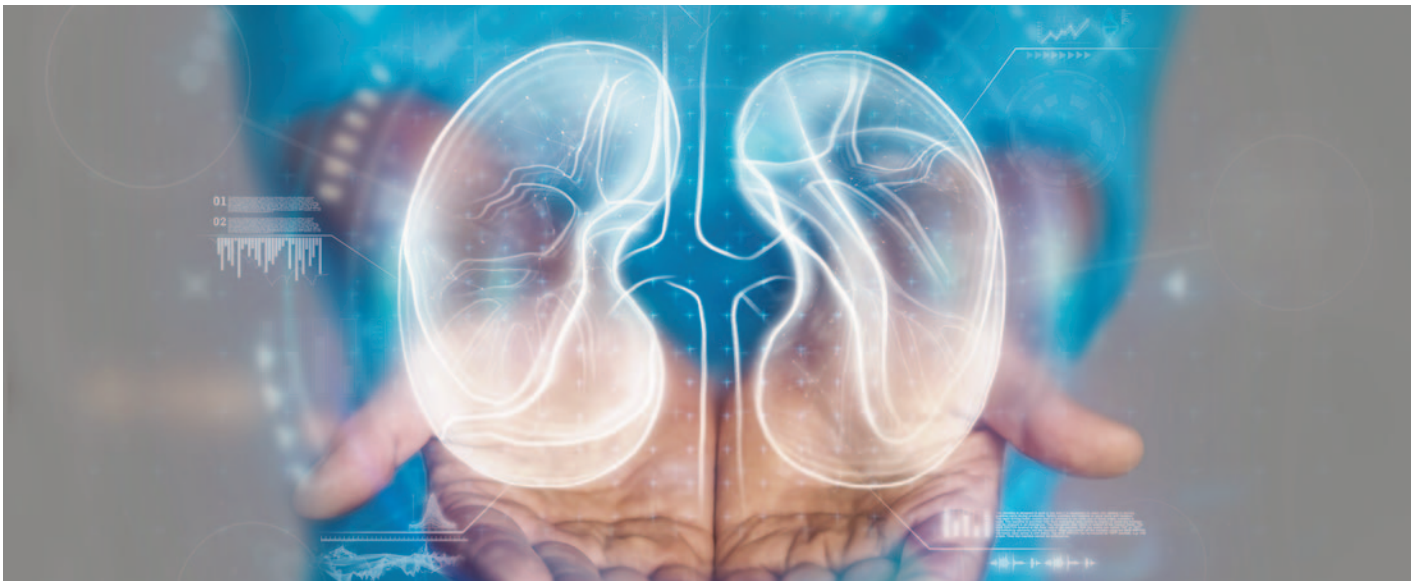
EMA's recommendation is based on the results of an ongoing multicentre, phase 3, single-arm, open-label clinical trial. The study investigated the efficacy and safety of tabelecleucel in 43 patients with relapsed/refractory EBV+ PTLD who had received at least one prior therapy. Approximately half of the treated subjects achieved partial or complete remission. A significant number of patients enrolled in the study responded to the treatment with a durable response of six months or more without disease signs or symptoms after treatment. The most common side effects are fever, diarrhoea, tiredness, feeling sick, low levels of red blood cells, decreased appetite, and low blood sodium levels.

In its overall assessment of the available data, the Committee for Advanced Therapies (CAT), EMA's expert committee for cell and gene-based medicines, found that the benefits of Ebvallo outweighed the risks in patients with EBV+ PTLD.

The CHMP agreed with the CAT's assessment and positive opinion, and recommended approval of this medicine under exceptional circumstances. A marketing authorisation under exceptional circumstances allows patients' access to medicines that cannot be approved using a standard authorisation route as comprehensive data cannot be obtained under normal conditions of use. Sometimes this is due to the small number of patients with the disease. In other cases, the collection of complete information on the efficacy and safety of the medicine is not possible or would be unethical. The medicines concerned are subject to specific post-authorisation obligations and monitoring.

The CHMP requested the applicant to submit data to further characterise the long-term efficacy and safety of patients enrolled in the clinical trials, and to conduct a post-authorisation observational safety study in patients treated with the medicine in Europe. The protocol must be submitted within three months of marketing authorisation.

The opinion adopted by the CHMP is an intermediary step on Ebvallo's path to patient access. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on the EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.



EMA confirms recommendation to withdraw marketing authorisations for amfepramone medicines

November 11, 2022

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has confirmed its recommendation to withdraw the marketing authorisations for amfepramone obesity medicines. This follows a re-examination of its previous recommendation of June 2022, which was requested by the companies that market these medicines.

Amfepramone is a sympathomimetic, which means that it acts in the brain and causes effects that are similar to those of adrenaline. Such medicines reduce a feeling of hunger. Amfepramone medicines are currently authorised in Denmark, Germany and Romania as treatment for patients with obesity (body mass index of at least 30 kg/m^2) in whom other weight-reduction methods have not worked on their own. Amfepramone medicines were authorised to be used for 4 to 6 weeks and no longer than 3 months.

The recommendation follows a review which found that measures to restrict the use of these medicines for safety reasons have not been sufficiently effective. It found that the medicines were being used for longer than the recommended maximum period of 3 months, thereby potentially increasing the risk of serious side effects such as pulmonary arterial hypertension (high blood pressure in the lungs) and dependency. The medicines were also being used in patients with a history of heart disease or psychiatric disorders, increasing their risk of heart and psychiatric problems. In addition, there was evidence of use during pregnancy, which could pose risks to the unborn baby.

The review considered all available information relating to these concerns, including data from two studies on the use of amfepramone medicines in Germany and in Denmark. In addition, the PRAC received advice from a group of experts, comprising endocrinologists, cardiologists, and a patient representative.

The PRAC considered introducing further measures to minimise the risk of side effects but could not identify any that would be sufficiently effective. The PRAC therefore concluded that the benefits of amfepramone medicines do not outweigh their risks and recommended that the medicines be removed from the market in the EU.

The PRAC recommendation will now be sent for its consideration to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). A direct healthcare professional communication (DHPC) will be sent in due course to healthcare professionals prescribing or dispensing the medicine and published on a dedicated page on the EMA website.

Sales of antibiotics for animal use have almost halved between 2011 and 2021

November 18, 2022

EMA's annual report on the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) shows that, since 2011, European countries have substantially reduced sales of veterinary antibiotics in animals. According to data from 25 countries that continuously provided input for the full 2011–2021 period, overall sales of veterinary antibiotics decreased by 47% in this interval, reaching the lowest value ever reported.

Sales of antibiotic classes considered critically important in human medicine also decreased noticeably between 2011 and 2021 and accounted for only 5.5% of total sales in 2021. Sales of third and fourth generation cephalosporins dropped by 38%, polymyxins by 80%, fluoroquinolones by 14% and sales of other quinolones dropped by 83%. These antibiotics should be used prudently and responsibly to preserve their effectiveness and mitigate the potential risk to public health, as indicated in the Antimicrobial Advice ad hoc Expert Group (AMEG) categorisation.

This ESVAC report includes, for the first time, information on the progress made towards the European Commission's Farm to Fork Strategy target to reduce the sale of antimicrobials for farmed animals and aquaculture in the EU. In only three years, between 2018 and 2021, the 27 EU Member States have already achieved a 18% reduction, approximately one third of the 50% reduction target set for 2030.

The Farm to Fork Strategy is at the core of the European Green Deal and aims to make food systems fair, healthy, and environmentally friendly. For each country participating in the ESVAC project there is a separate section presenting sales trends by antimicrobial class. Some countries describe their main measures to address antimicrobial resistance and how these activities contribute to the observed changes in sales in their country. The measures include national action plans, national campaigns for prudent use of antimicrobials in animals, restrictions on the use of certain antimicrobials in food-producing animals, or measures to control prescription of antimicrobials in animals.

The twelfth ESVAC report presents data from 31 European countries (29 EU/EEA countries, Switzerland and the United Kingdom). All participating countries voluntarily provided information on sales of veterinary antimicrobials. The ESVAC project was launched by EMA in September 2009 following a request from the European Commission. Since then, the Agency has coordinated and supported European countries' efforts to establish standardised and harmonised reporting on the volume of sales of veterinary antimicrobial medicinal products. The ESVAC report is published annually and is used as a reference source of information for scientists, veterinarians and other health professionals, risk assessors, and policy makers in the EU Member States.

Under Regulation (EU) 2019/6, reporting data on the sales and use of antimicrobials in animals will become a legal obligation for EU Member States and the Agency. The new requirements will apply to data from 2023 onwards.

DARWIN EU® welcomes first data partners

November 23, 2022

EMA has selected the first set of data partners to collaborate with DARWIN EU®, the Data Analysis and Real-World Interrogation Network. The data available to these partners will be used for studies to generate real-world evidence that will support scientific evaluations and regulatory decision making. Real-world evidence refers to information derived from analysis of real-world data, which is routinely collected data about a patient's health status or delivery of healthcare from a variety of sources other than traditional clinical trials.

The selected partners include both public and private institutions. The common feature is that they all have access to real-world healthcare data from one or more sources such as hospitals, primary care, health insurance, biobanks, or disease-specific patient registries. The data partners will provide the DARWIN EU® Coordination Centre with results of analyses of these data.

With the onboarding of data partners, EMA has initiated the launch of the first three studies to be provided by DARWIN EU®. One study will focus on the epidemiology of rare blood cancers to inform on their prevalence in Europe. The second study is on drug use of valproate and the third one is looking at the use of antibiotics to inform future work on anti-microbial resistance. EMA will report more details of these studies in due course, including the publication of protocols and reports in the EU Post-Authorisation Studies (PAS) register. These studies mark the start of a rapid ramp-up in the number of studies conducted to support regulatory decision making. The aim is that by 2025 DARWIN EU ® will deliver approximately 150 real-world evidence studies per year.

Data partners were selected according to prioritisation criteria after consultation with the DARWIN EU® Advisory Board. According to these criteria:

Sources should have continuous data collection with at least annual data updates, a lag time of less than six months in data availability for analysis and capture of health outcomes and medicines prescribing or dispensing.

The data should be available already converted into the Observational Medical Outcomes Partnership OMOP Common Data Model (CDM), which allows analyses to be performed using the same analytical code.

Data sources should represent different healthcare settings of medicines use (primary, secondary, specialist use) as well as, collectively, the EU population. Non-EU data sources can be considered for inclusion if they add value to real-world evidence analyses and enrich the results for decision making on medicines.

The number of data partners will increase in the coming years. The target is to add at least ten new data partners every year. In 2023, a call for expressions of interest for potential new data partners will be launched.

DARWIN EU® is a federated network which gives the European medicines regulatory network, composed of national competent authorities in the EU Member States, EMA and the European Commission, access to results from analysis of data from real-world healthcare databases across the EU whenever needed and supporting decision making throughout the lifecycle of a medicine. Thus, DARWIN EU® enables more informed regulatory decision making.

Knowledge of diseases, of medicines use and of how medicines perform in clinical practice can inform regulatory decision making and support the development, authorisation, and safe and effective use of medicines by patients.

EMA manages DARWIN EU® and oversees the Erasmus University Medical Center Rotterdam which was appointed as the DARWIN EU® Coordination Centre in February 2022. The network will act as a pathfinder for the proposed European Health Data Space (EHDS), and will ultimately connect to the EHDS services, enabling the use of the EHDS in medicines regulation in Europe.

Facilitating decentralised clinical trials in the EU

December 19, 2022

The European Commission (EC), the Heads of Medicines Agencies (HMA) and the EMA have published recommendations that aim to facilitate the conduct of decentralised clinical trials (DCTs) while safeguarding the rights and well-being of participants as well as the robustness and reliability of the data collected (https://health.ec.europa.eu/system/files/2022-12/mp_decentralised-elements_clinical-trials_rec_en.pdf). This is an outcome of their joint initiative to Accelerate Clinical Trials in the European Union (ACT EU).

Traditionally, clinical trials have been conducted at specific clinical trial sites, to which patients had to travel. The aim of DCTs is to make it easier for patients to participate in clinical trials by reducing the need to travel to central trial sites. This approach has the potential to make clinical trials available to a wider demographic of participants and reduce drop-out rates.

Decentralisation is enabled by the advancement of digital tools, telemedicine, and more mobile and local healthcare. It includes aspects such as home health visits, remote monitoring and diagnostics, direct-to-patient shipment of study drugs, and electronic informed consent.

The recommendations include an overview of national provisions for specific decentralised clinical trial elements to be used in clinical trials. They were put together by the European medicines regulatory network with experts from regulatory bodies responsible for the authorisation of clinical trials, members of ethic committees, good clinical practice inspectors, methodology experts and representatives of patient organisations. Drafting of the paper was coordinated by the clinical trials coordination group (CTCG).

These recommendations under ACT EU are a first and important step towards clarifying the use of decentralised clinical trials in the EU/EEA by the European medicines regulatory network. They are expected to evolve as knowledge increases and experience is gained. In particular, the overview of national provisions will be updated on a continuous basis.

ACT EU initiative was launched in January 2022 and aims to further develop the EU as a focal point for clinical research, to promote the development of high-quality, safe and effective medicines, and to better integrate clinical research in the European health system. ACT EU will strengthen the European environment for clinical trials, whilst maintaining the high level of protection of trial participants, data robustness, and transparency that EU/EEA citizens expect. ACT EU features ten priority action areas that are the basis for the ACT EU 2022–2026 workplan.

Teaching Medical Writing

SECTION EDITOR

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Few universities offer courses in medical writing, and students from the biomedical sciences who wish to become medical writers typically need to learn written communication skills on the job. These skills are extremely varied and include:

- Critical analysis of data in scientific reports and publications
- Appropriate synthesis of large amounts of information from diverse sources
- Ability to write well-structured texts that are clear, accurate, and grammatically correct
- Understanding the needs of different target audiences
- Awareness of legal and ethical issues such as transparency and plagiarism.

It would be hugely advantageous to learn these skills through an accredited university course that enabled discussion, collaboration, and review of each other's texts.

In this article, Joanna Verran and colleagues provide a fascinating insight into the opportunities and challenges when establishing a Medical Writing course at postgraduate level. The course is particularly interesting due to its development through a collaboration between the university and representatives from MedComms companies.

Happy Reading!

Claire

Co-development, co-delivery, and evaluation of a Medical Writing module at master's level

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Introduction

The introduction of an MSc in Science Communication at Manchester Metropolitan University, UK, provided the opportunity to co-develop and co-deliver a Medical Writing module with representatives from a range of MedComms companies. This module was included as an option within the MSc programme. Student feedback was good, and most of the students who took the module gained employment within the industry. The development process, content, delivery, assessment, evaluation, and the future of the module are addressed in this article.

In a jobs-focused university environment, it is important that students learn not only the appropriate skills but also the relevant knowledge of potential employers.[1] For students of the biomedical sciences, obvious post-graduation routes include the professionally accredited biomedical science routes for teaching, research, and laboratory-focused work within academia and the pharmaceutical, food, environmental, and other industries.[2] However, the world of medical communications (MedComms) is far from the typical science graduate experience.

As university academics, we were aware of MedComms professions primarily through employment of our past PhD students. We noted how these students brought their science literacy, knowledge, expertise, and skills to a career beyond the laboratory. We felt that we, in turn, should bring this important employment opportunity to a wider student audience.

Increasing numbers of universities are offering master's courses in Science Communication.

Increasing numbers of universities are offering master's courses in Science Communication.[3] Each of these tends to focus on the specialist expertise offered by the host university, thus it is important to be able to market an "angle" to attract applicants to a given course.

At Manchester Metropolitan University (MMU), in addition to an active team delivering events and activities designed to enhance public understanding of science, a healthy research-focused publication output on science communication is evident.[4–6] Cross-disciplinary collaboration between the humanities and the sciences is also well-established,[7–10] enabling the development of an Art and Science module within a new MSc in Science Communication. The Department of Life Sciences within the Faculty of Science and Engineering has a large and very well-respected Biomedical Science research and teaching (undergraduate and postgraduate) portfolio, which facilitated the development of a unique Medical Writing module. Thus, a new MSc in Science Communication was devised, incorporating these particular areas of expertise alongside more fundamental aspects of the discipline.

This paper describes how we brought together our higher education expertise with the expertise of the MedComms profession to develop and deliver a postgraduate module in Medical Writing. This module was part of the MSc in Science Communication, but it was also offered as a standalone module for interested individuals.

Course approval

To deliver a new university course, the staff proposing it are required to demonstrate a need/demand (thus attracting students and

securing funding) and the availability of appropriate expertise and staff time for delivery, preferably accompanied by letters of support from various stakeholders. In developing the MSc, the Science Communications team at MMU used a student intern to conduct some market research on likely recruitment, which highlighted the proposed module in Medical Writing as one of the unique selling points for such a course. The course proposal was approved though the formal university procedure, and development went ahead.

The MSc was designed to be delivered over 12 months full-time (or 24 months part-time) and consisted of four 30-credit modules and one 60-credit module (Figure 1). Students were given the option of picking one module from either Science Journalism, Medical Writing, or SciArt, depending on the area they wished to specialise in. The Medical Writing module is the focus of this paper.

Module development

It was essential that the MedComms community both supported the module and could provide input into it, so a network was assembled – initially via contact with ex-students and other colleagues working in the area, thence to the European Medical Writers Association (EMWA), the International Society for Medical Publication Professionals (ISMPP), and Network Pharma. A presentation was given at the EMWA meeting in 2016 to raise awareness of the course and module, followed by a call from Network Pharma. It is fortunate that the Northwest of England is home to a large number of pharma companies, but it is also fantastic how many companies and individuals from other regions of the country became such committed collaborators in this new venture. (Several contacts provided letters of support for submission to the course approval committee, and while some reservations were expressed regarding the academic level of the course – recruitment tends to be at PhD level rather than master's level – all were willing to explore the option.)

Ultimately, 19 representatives from 18 different companies became the industrial liaison team, alongside the four university academics (and authors of this paper) who formed the course management team. After initial contact had been made, the industrial partners were provided with the course objectives, learning outcomes, assessments, and indicative content of the Medical Writing module that had been used to obtain preliminary course approval (Figure 2). They were asked to help develop these with more

Figure 1. The modules for the MSc Science Communication course

The three blue modules were each worth 30 credits, and the yellow module ("Live Projects") was worth 60 credits. Students then chose one 30-credit green module (Science Journalism, Medical Writing, or SciArt). Practical Science Communication and a "green" module were delivered in Term 1; Science Communication as an Academic Discipline and Science and Society were delivered in Term 2; the live project took place during the remainder of the academic year.

Session	Topic	Staff	Indicative content
Enrol	MedComms Conference[a] (open attendance)		
L1	The World of Medical Writing	A[b]/I	Brief overview of medical communications from industrial partners, outlining some of the different routes through the profession, commercial considerations, and giving an overview of desirable employee attributes. Consideration will be given to how to manage a project from initiation to final sign-off.
S1	Preparation for Assignments	A	Assignment requirements and recommendations will be outlined. Introductions via a personal statement, and as a beginning to CV/portfolio development. This written work will also be collected in and edited if appropriate. Editing exercise.
L2	Clinical Development Process I	I	An overview of the clinical development process – including pre-clinical stages – as underpinning information to support understanding of the profession. Pharmacokinetics refresher.
S2	Digital Comms	A	Digital communications. Online publishing. LinkedIn, Twitter, etc. Portfolio/reflective diaries.
L3	Clinical Development Process II	I	Outline of overall process, with illustrative examples. Marketing access (pricing, reimbursement), as well as marketing approval, and phase 4 post-marketing, pharmacovigilance, and real-world observational studies.
S3	Clinical Development Activity	I	Activities illustrating clinical development process.
L4	Writing Good English	A	The value of writing well, and the principles of basic English and grammar (University Language Centre). Consideration as to how all interactions with others contribute to an impression of professionalism (emails, webex, telephone).
S4	Writing for Different Audiences	A	The different ways in which English might be used to communicate information around medical research (social media, press, narrative) to a range of different audiences.
L5	Core Medical Writing Skills I	I	The conventions of scientific writing, and how to read, abstract, and present scientific/technical information in writing. The session will include reference management, abstracting information, writing abstracts, working to time constraints. Introduction to typical expectations of a project brief and subsequent outputs, and the role in setting standards of relevant professional groups such as ISMPP, EMWA. Guidelines for manuscript preparation, and reporting of different types of clinical data as provided by the EQUATOR network. Good publication practice guidelines (GPP) and reporting guidelines (e.g., CONSORT).
S5	The Craft of Copywriting	I	In this externally led session, tips, tricks, and exercises to hone your writing skills and make your copy compelling and irresistible to read will be given.
L6	Core Medical Writing Skills II: Information retrieval and management	A	The range of information resources available, including core medical writing resources – journals, papers, website, databases, textbooks (with University Library)
S6	Assignment one workshop	A	
L7	Statistics and Presentation of Data I	A	A refresher on the basic statistical analyses used in clinical research, to help understanding and interpretation of results.
S7	Statistics and Presentation of Data II	A	How best to present information derived from clinical data, including digital channels, PowerPoint, Prezi, Keynote, tables, infographics, etc.

Session	Topic	Staff	Indicative content
L8	Clinical Studies: Interpretation and presentation of clinical data	A	Bringing previous topics together with examples and exercises.
S8	Assignment workshop		
	Assignment one deadline		
L9	Professional Standards: Constraints and Compliance	I	The context within which the profession operates, including the need to focus on good publication practice, adverse event reporting, copyright infringement, plagiarism, data protection, etc. as well as business ethics, professionalism, and responsibility. Regulatory bodies/guidelines such as EFPIA, ABPI, ICMJE, GPP3, Sunshine Act, EQUATOR Network.
S9	Case Studies	I	Different case studies which raise issues around constraints and compliance (e.g., authorship, disclosure, copyright, plagiarism, ethics, code of conduct) will be provided for consideration and discussion.
L10	Communicating with different audiences	I	A different look at how audiences perceive and understand modes of communication.
S10	Assignment two workshop	A	
	Placement week		
L11	Understanding new therapy areas	A/I	Introduction to relevant hot topics by healthcare science researchers at the University, and consideration as to how information around these topics can be converted into appropriate resources, for different audiences such as specialists, healthcare providers, internal pharma, patients, etc. A request for proposals (RFP) will be provided for students to present during Thursday's session, with a Q&A session to help clarify the RFP.
S11	Responding to a brief: Student presentations	A/I	Students make a pitch, with up to five slides (or no slides) in a "Dragons Den" format on the basis of Tuesday's RFP
L12	One-to-one tutorials	A	
	Professionalism	I	Writing test, CV surgery, careers overview, Q&A

Table 1. The structure and indicative content of the Medical Writing module within the MSc Science Communication at Manchester Metropolitan University

Week numbers 1–12 are designated L=Lecture or S=Seminar. A range of student-centred activities took place throughout the lecture and seminar slots.

a The conference/event was organised by Network Pharma and hosted by the University of Manchester.

b A member of the academic staff (A) was in attendance at all sessions. Joint delivery (A/I) is specified. Other sessions were led/delivered by representatives from Industry (I).

Abbreviations: ISMPP, International Society for Medical Publication Professionals; EFPIA, European Federation of Pharmaceutical Industries and Associations; ABPI, Association of the British Pharamceutical Industry; ICMJE, International Committee of Medical Journal Editors; GPP3, Good Publication Practice 3; EQUATOR, Enhancing the QUALity and Transparency of health Research.

detailed suggestions regarding content. This preliminary information and feedback were used during an "awayday" where the module structure was built. At this developmental meeting, participants were informed as follows:

> "At this meeting, we will outline the overall course aims, content, and learning objectives so that you will be able to see the context in which the Medical Writing route will operate. For the Medical Writing module, we will consider content, delivery methods, formative, and summative assessments. There will also be opportunity to consolidate the relationship between this module and the live project."

The format of the day comprised morning and afternoon breakout sessions followed by pooling of ideas and iterative construction of the module in terms of content, sequence, student activity, and assessment. Information that industrial partners provided prior to the awayday proved particularly useful to the academic staff in terms of the wide-ranging scope of desirable and

Module description

This module will introduce you to medical writing as a profession and provide you with the skills and knowledge that are necessary for a career within a medical communications provider/agency – as well as for a range of other professions requiring excellent communication skills.

The curriculum will cover:

- The interpretation of clinical data and the critical analysis of publications containing such data
- An overview of the industry and profession
- The legal framework within which the industry operates
- An overview of the different audiences towards which medical communications are aimed
- Effective, accurate, and grammatically correct writing of scientific/medical content to a brief, aimed at scientifically literate audiences encompassing journal publication, conferences, print publications, digital publication, video, and audio content.

This module has been designed in conjunction with a number of medical communications companies, meaning that upon graduation students that have elected to study this module will be extremely well placed in terms of employment prospects in medical communications.

Learning outcomes

On successful completion of this module, you will be able to:

1. Assess the scientific importance of clinical research outputs with reference to the effectiveness of pharmaceutical products;
2. Distinguish between the needs and requirements of different audiences and delivery platforms/methods when writing medical communications;
3. Compose a piece of evaluative medical writing, written to a brief.

(ASSIGNMENT 1):

Report on clinical paper (30% of total assessment mark)

You will be given more detailed instructions at the beginning of the course.

You must critically analyse the scientific content within a journal publication containing clinical data relating to the development of a pharmaceutical product. This might be suggested to you by a tutor, or an industrial partner, or you might identify your own publication (and seek tutor agreement for appropriateness). From this, you will produce a report detailing:

- An overview of the therapeutic area
- A consideration of existing drugs used in this therapeutic area
- An analysis of the drug under development, including a consideration of the evidence for its efficacy
- The therapy area, the range of drugs already on the market, and the product that the data are supporting
- An analysis of the scientific evidence.

(ASSIGNMENT 2):

Portfolio (70% of total assessment mark)

You will be given more detailed instructions at the beginning of the course.

Create a portfolio of medical communications/writing that has been constructed to a brief, based on a clinical research paper regarding a pharmaceutical product. You will be expected to:

- Critically analyse the publication
- Reconstruct the data into one or more elements of communication for a range of target audiences, e.g. clinicians, nurses, patients etc.
- Discuss your approach to different styles of writing for each of the elements and target audiences
- Ensure that all elements produced meet the legal and ethical framework within which UK medical writing must comply.

Figure 2. An extract from the student handbook, providing an overview of the Medical Writing module

essential skills required.

Free and open discussion enabled the development of a module with which all participants were satisfied – one that was sufficiently rigorous for master's level, had assessments appropriate to module aims, and encompassed a broad overview of the MedComms industry and the scientific writing and presentation skills necessary. A summary of the discussion and the module structure was circulated for comment. This was then refined over a couple of months so that the module was deemed satisfactory by all participants and was ready for delivery (Table 1).

Representatives from different companies took ownership for different sessions (often companies shared delivery). Indeed, several of the awayday participants noted how enjoyable it was to work with colleagues from other companies. Additional benefits were the collaboration with university academics and the opportunity to formally become "Associate Lecturers".

Module delivery and evaluation

The course was advertised through the usual university postgraduate portfolio (including a video) and at recruitment open days. Advertisements were also circulated via Network Pharma. The first cohort on the Medical Writing module comprised four students, of which one was taking the course part-time, and another (PhD student) was taking the module as a free-standing unit. The remainder were recent graduates. The second cohort comprised seven students (more students registered for the MSc overall for both cohorts, but numbers were low overall; the Science and Art module option was selected by all other students).

The Medical Writing module was delivered over one semester (12 weeks) for five hours per

week (three hours of lecture-based sessions and workshops on a Tuesday, and two hours of seminar-focused interactive sessions on a Thursday).

Every session was attended by a member of the academic staff. (The first cohort was attended by author Joanna Verran; the second cohort by author James Pritchett) to provide continuity and to observe and learn further about the profession. Communication within the industrial liaison team was regular and frequent.

Student attendance was excellent; it seemed evident to the students that such an intensive module required commitment. Industrial partners who delivered sessions noted that student participation was initially poor – there seemed to be some reticence to join discussion in a small group – but this improved as the module progressed and students gained confidence. There was also interesting crossover for some companies as they learned more about the course overall. For example, the SciArt module exhibition showcased students with overt artistic talents that enabled additional collaboration[11] (see e.g. Figure 3).

Summative assessments were supported throughout the module by formative assessments and other exercises. Tutorials and workshops also provided support for assignments. A particular success of the module was the work placement week, for which students were required to research the partner companies, select two where they wanted to work, and write an application letter. This was fairly intensive work for the academic placement tutor (and would have been very significant with a larger student cohort). A particularly (intentionally) stressful session was the "responding to a brief" event, where students had to translate research presentations from university researchers into pitches for drug marketing within 48 hours.

Student evaluation was detailed and constructive, enabling the industrial liaison team to review the delivery of the module and make any appropriate modifications. The students were keen for even more opportunities to practise writing for different audiences.

Summative assessments were supported throughout the module by formative assessments and other exercises.

Outcomes

For the first cohort of students, all were employed by a pharmaceutical company within six months of graduation, predominantly by the company in which they had undertaken their work experience. Feedback from the students was very positive.

One noted:

"Before I started my MSc in Science Communication and Medical Writing submodule, I was completely unaware of the Med Comms industry that I now find myself in.

During the course I learnt how to transform complex science into understandable information for a variety of different audiences. This came in useful during my live project, where I conducted a narrative review into methods of reflection for medical students.

Since then, I've worked at two Med Comms companies, in Europe and London, and authored a publication. A big 'Thanks' goes out to the course leaders for giving me the tools to achieve this!"

And another:

"The MedComms module has hugely benefitted my career by providing a strong foundation on which to develop my skills ahead of beginning my career in MedComms. I was grateful for the depth of information and insights provided about all aspects of working on MedComms, and for the opportunity to hear from different lecturers and speakers who provided their own working experience and direct guidance, which may not always be available for those just starting out in MedComms as many scientific graduates may not have heard of MedComms careers during their studies. I am now happily working in MedComms."

Some of the students chose to do their Live Project in collaboration with one of the companies, with a university supervisor to guide the academic dimensions and ensure that learning objectives were met. In addition to the overall grades of the module, there were further benefits in that some of the students presented their work at conferences, and others had their work published in peer-reviewed journals (students Clausi and Silvagnoli[12–14]).

Despite these successes, the MSc Science Communication was unfortunately discontinued after two iterations, primarily because low student numbers made it unsustainable. Poor recruitment may have resulted from difficulties in marketing the course to the appropriate target audience, amongst competition from other more well-known postgraduate routes. The academic and industrial liaison team subsequently considered the possibility of developing an online module/course based on and further developing the experience from the Medical Writing module, but this did not progress.

Despite the discontinuation of the module, the delivery team considered that the collaborative design, delivery, and evaluation, combined with the evident academic and professional success of the students, merited dissemination. This was the motivation for writing this paper. There are other avenues for training in medical writing – EMWA and several pharma companies provide various training units or open access modules to prepare potential applicants/update existing employees. Some universities offer Medical Writing courses,[15–16] but these are few. It is therefore hoped that the lessons learned, and the content developed, may help others who are thinking about designing courses to educate students in the world of medical writing.

Summary: Lessons learned

- University accreditation and validation procedures provide appropriate rigour and robust evidence of learning at master's level.
- Collaboration between university and industry is essential for module development and delivery, and it is highly enjoyable and enlightening.
- Students respond well to a Medical Writing module, and they are eminently employable in the field.
- The module is costly in terms of staff time (university and industry), irrespective of student numbers, and face-to-face delivery requires several lecturers with different expertise each time the course is run.
- It is essential that advertising and marketing

Figure 3. Artist Tony Pickering collaborated with St Giles Med to showcase his experiences with type 1 diabetes.

reaches the intended audience.

- All stakeholders need to be committed to maintain delivery and ensure sustainability of the module over time.
- We consider that the module development, content, delivery, assessment and evaluation described herein is an example of good practice.
- There is potential for online delivery of an accredited module.

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The authors declare no conflicts of interest

References

1. Wickramasinghe V, Perera L. Graduates', university lecturers', and employers' perceptions towards employability skills. Educ Train. 2010 Apr 27.
2. Zimmerman AM. Navigating the path to a biomedical science career. PloS One. 2018;13(9):e0203783. doi:10.1371/journal.pone.0203783
3. Mellor F. Twenty years of teaching science communication: A case study of Imperial College's master's programme. Public Underst Sci. 2013;22(8):916–26. doi:10.1177/0963662513489386
4. Illingworth S, Redfern J, Millington S, Gray S. What's in a name? Exploring the nomenclature of science communication in the UK. F1000Research. 2015;4:409. doi:10.12688/Ff1000research.6858.2
5. Redfern J, Bowater L, Coulthwaite L, Verran J. Raising awareness of antimicrobial resistance among the general public in the UK: The role of public engagement activities. JAC Antimicrob Resist. 2020;2(1):dlaa012. doi:10.1093/jacamr/dlaa012
6. Redfern J, Illingworth S, Verran J. What does the UK public want from academic science communication? F1000Research. 2016;5:1261. doi:10.12688/f1000research.8815.1
7. Illingworth S, Griffiths D. SciArt: Teaching across the interface. EOS: Earth and Space Science News. 2019 Jan 29.
8. Illingworth S, Jack K. Rhyme and reason – using poetry to talk to underserved audiences about environmental change. Clim Risk Manag. 2018;19:120–9. doi:10.1016/j.crm.2018.01.001
9. Verran J. Using fiction to engage audiences with infectious disease: The effect of the coronavirus pandemic on participation in the Bad Bugs Bookclub. FEMS Microbiol Lett. 2021;368(14):fnab072. doi:10.1093/femsle/fnab072
10. Verran J. Mixed cultures: Encouraging cross-disciplinary collaboration and communication to enhance learning. Ann Microbiol. 2019;69:1107-11. doi:10.1007/s13213-019-01481-8
11. Pickering T. What your patient is drawing. BMJ. 2019;367. doi:10.1007/s13213-019-01481-8
12. Martínez Silvagnoli L, Shepherd C, Pritchett J, Gardner J. Optimizing readability and format of Plain Language Summaries for medical research articles: Cross-sectional survey study. J Med Internet Res. 2022;24(1):e22122 doi:10.2196/22122
13. Gardner J, Silvagnoli LMI, Shepherd C, Pritchett J. Evaluation of plain-language summaries (PLSs): Optimizing readability and format. Curr Med Res Opin. 2019; 35:36.
14. Clausi V, Shepherd C, Gardner J, et al. Do corresponding authors value the support of professional medical writers? Curr Med Res Opin. 2018;34:33.
15. Leventhal P. Medical writing education. Med Writ. 2013;22(1):1
16. Benau D. On educating the medical writer. Med Writ. 2013;22(1):26–8.

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Regulatory Public Disclosure

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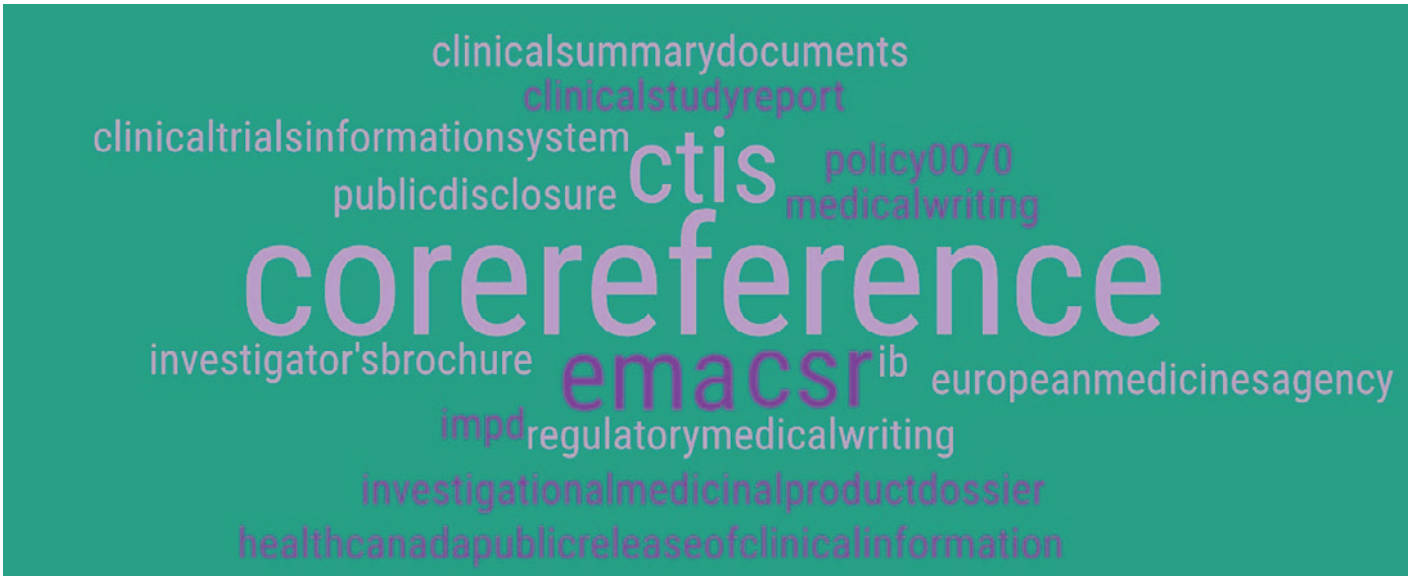

Editorial

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EU Clinical Trials Regulation and Clinical Trials Information System

It is now 14 months since the EU Clinical Trials Regulation (CTR) 536/2014 came into force at the end of January 2022. As of January 31, 2023, all sponsors of clinical trials became obliged to use the Clinical Trials Information System (CTIS) and follow the same process to apply for clinical trial authorisation in the EU/EEA. For individual companies, changes to and enhancements of processes have been necessary at the application stage of the clinical trial to support the use of the CTIS platform. Not all of the publicly disclosed documents fall under the ownership of medical writers now that this has broadened to include for example, the Investigator's Brochure and Investigational Medicinal Product Dossier (IMPD), and Risk Management Plan (RMP). This rather depends on individual company processes and document ownership responsibilities. However, the techniques that the regulatory medical writing function has employed for the past 6 years or so in creating proactively authored documents fit for public disclosure with minimal need for redaction, are proving invaluable. We have the opportunity to educate cross-functionally to ensure that Commercially Confidential Information (CCI) is excluded from documents that are going to find their way into the public domain – because most often CCI redactions are not permitted. Keep the mantra "if in doubt, leave it out" in mind at all times! Come and learn more about the impact of CTIS on medical writing at the Expert Seminar Series Session 3 on May 12, 2023 (morning) at the upcoming EMWA Conference in Prague. (The conference takes place May 9–13).

CESHARP – the (draft) ICH standard and template for protocols

Another major milestone was reached in September 2022 when ICH released a Step 2 draft guideline outlining a harmonised template for clinical trial protocols to support consistency among sponsors. The ICH M11 Clinical Electronic Structured Harmonised Protocol (CESHARP) draft guideline (https://database.ich.org/sites/default/files/ICH_M11_draft_Guideline_Step2_2022_0904.pdf), plus template (https://database.ich.org/sites/default/files/ICH_M11_Template_Step2_2022_0904. pdf) and template technical specifications (https://database.ich.org/sites/default/files/ICH_M11_TechnicalSpecification_Step2_2022_1014.pdf), were released for public consultation on October 21, 2022. The scope of ICH M11 is to establish common instructions for placement of content and information on technical attributes. According to ICH, "The guideline aims to have clinical trial protocol templates that are complete, free from ambiguity, well organised, and aligned with quality by design principles as set forth in other ICH guidelines." The template has a core set of information for clinical trials including fonts that should be used in the protocols, numbering for tables and figures, as well as acceptable abbreviations. The consultation period ended in February 2023, so watch out for the next release of this draft guideline and template, which should reflect end-user perspectives. In a related move, TransCelerate Biopharma released their "Clinical Template Suite (CTS) Release Addendum" in November 2022. This is a "track changes" clinical protocol template (CPT v009) with only limited updates. The addendum clarifies that the next round of TransCelerate templates will be released in the second half of 2023, to allow alignment with ICH M11 and EU PEARL – the EU patient-centric clinical trial platform

Table 1. TransCelerate CPT (v009, file dated October 12, 2022) versus Draft (Step 2) ICH M11 Template: A Comparison of Level 2 headings Published open access by the CORE Reference Project Team on December 13, 2022
https://www.core-reference.org/news-summaries/core-reference-project-team-compare-transcelerate-cpt-v009-and-draft-ich-m11-step-2-templates-a-comparison-of-level-2-headings

Level 1 heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 heading	Draft ICH M11 Level 2 heading	Brief comment
1 Protocol Summary	1.1 Synopsis 1.2 Schema 1.3 SoA	1.1 Protocol Synopsis 1.2 Trial Schema 1.3 SoA	Similar overall structure
2 Introduction	2.1 Study Rationale 2.2 Background 2.3 Benefit/Risk Assessment	2.1 Purpose of Trial 2.2 Summary of Benefits and Risk	Similar level of detail required
3 Trial Objectives, Endpoints and Estimands	Primary estimand/ coprimary estimands/ multiple primary estimands (non-numbered Level 2 heading) Secondary estimands (non-numbered Level 2 heading)	3.1 {Primary/Secondary/Exploratory} Objective + Associated Endpoint {and Estimand}	Although no definitive Level 2 headings are provided, more comprehensive guidance regarding how endpoints and objectives should be presented is proposed in the TransCelerate template than is provided in the M11 template
4 Trial Design	4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose 4.4 End of Study Definition	4.1 Description of Trial Design 4.2 Rationale for Trial Design 4.3 Access to Trial Intervention After End of Trial 4.4 Start of Trial and End of Trial	Draft ICH M11 requires description of any possibilities for access to trial intervention, beyond completion of the trial (Found in Section 6.7 in TransCelerate CPT)
5 Trial Population	5.1 Inclusion Criteria 5.2 Exclusion Criteria 5.3 Lifestyle Considerations 5.4 Screen Failures 5.5 Criteria for Temporary Delaying Enrollment/ Randomisation/ Administration of Study Intervention	5.1 Selection of Trial Population 5.2 Rationale for Trial Population 5.3 Inclusion Criteria 5.4 Exclusion Criteria 5.5 Lifestyle Considerations 5.6 Screen failures	Draft ICH M11 specifically addresses the selection and rationale for the study population TransCelerate template includes Section 5.5 which is not indicated in Draft ICH M11
6 Trial Intervention and Concomitant Therapy	6.1 Study Intervention Administered 6.2 Preparation, Handling, Storage and Accountability 6.3 Assignment to Study Intervention 6.4 Blinding/masking 6.5 Study Intervention Compliance 6.6 Dose Modification 6.7 Continued Access to Study Intervention after End of the Study 6.8 Treatment of Overdose 6.9 Prior and Concomitant Therapy	6.1 Description of Trial Intervention 6.2 Rationale for Trial Intervention 6.3 Dosing and Administration 6.4 Treatment of Overdose 6.5 Preparation, Handling, Storage and Accountability 6.6 Participant Assignment, Randomisation and Blinding 6.7 Trial Intervention Compliance 6.8 Concomitant Therapy	Overall organisation of information differs slightly between the 2 templates

Level 1 heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 heading	Draft ICH M11 Level 2 heading	Brief comment
7 Discontinuation of Trial Intervention and Participant Withdrawal from Trial	7.1 Discontinuation of Study Intervention 7.2 Participant Discontinuation/Withdrawal from the Study 7.3 Lost to Follow up	7.1 Discontinuation of Trial Intervention 7.2 Participant Withdrawal from the Trial 7.3 Lost to Follow-Up 7.4 Trial Stopping Rules	Draft ICH M11 emphasises the need to describe trial-specific stopping rules, e.g., guidance on stopping trial for safety reasons, when a cohort or dose escalation should be terminated, and/or treatment arm terminated Notably, TransCelerate does consider specific participant stopping rules based on different variables, e.g., liver chemistry stopping criteria, QTc stopping criteria in Section 7.1 as Level 3 headings, but there is no guidance on stopping a trial/treatment arm
8 Trial Assessments and Procedures	8.1 Administrative and General/Baseline Procedures 8.2 Efficacy and/or Immunogenicity Assessments 8.3 Safety Assessments 8.4 Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting 8.5 Pharmacokinetics 8.6 Pharmacodynamics 8.7 Genetics 8.8 Biomarkers 8.9 Immunogenicity Assessments 8.10 Health Economics OR Medical Resource Utilisation and Health Economics	8.1 Screening/Baseline Assessments and Procedures 8.2 Efficacy Assessments and Procedures 8.3 Safety Assessments and Procedures 8.4 Adverse Events and Serious Adverse Events 8.5 Pregnancy and Postpartum Information 8.6 Medical Device Product Complaints for Drug/Device Combination Products 8.7 Pharmacokinetics 8.8 Genetics 8.9 Biomarkers 8.10 Immunogenicity Assessments 8.11 Medical Resource Utilisation and Health Economics	Draft ICH M11: Section 8.6 is an additional optional section. Notably, in TransCelerate template Medical Device Deficiencies is a Level 3 heading (Section 8.4.9) and further medical device information is included in Appendix 7 Draft ICH M11: Pharmacodynamics level 2 heading present in TransCelerate template (Section 8.6) is not included Notably, while Draft ICH M11 considers Pregnancy as a separate Level 2 heading (Section 8.5), it is a Level 3 heading (Section 8.4.5) in the TransCelerate template

(Continued on next page)

Table 1 (Continued)

Level 1 heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 heading	Draft ICH M11 Level 2 heading	Brief comment
9 Statistical Considerations	9.1 Statistical Hypothesis/Hypotheses 9.2. Analysis Sets 9.3. Statistical Analyses 9.4. Interim Analysis/Analyses 9.5. Sample Size Determination	9.1 Analysis Sets 9.2 Analyses Supporting Primary Objective(s) 9.3 Analysis Supporting Secondary Objective(s) 9.4 Analysis of Exploratory Objective(s) 9.5 Safety Analyses 9.6 Other Analyses 9.7 Interim Analyses 9.8 Sample Size Determination 9.10 Protocol Deviations	Although draft ICH M11 uses detailed level 2 structure for the presentation of statistical analyses and considerations, the information covered in the statistical section is generally similar between the two templates Draft ICH M11 Section 9.10 Protocol Deviations is an additional section compared with the TransCelerate template
10 General Considerations: Regulatory, Ethical, and Trial Oversight	10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 10.2. Appendix 2: Clinical Laboratory Tests 10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 10.4. Appendix 4: Contraceptive and Barrier Guidance 10.5 Appendix 5: Genetics 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines 10.7. Appendix 7: Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies 10.8. Appendix 8: Country-specific Requirements 10.9 Appendix 9: Protocol Amendment History	10.1 Regulatory and Ethical Considerations 10.2 Committees 10.3 Informed Consent Process 10.4 Data Protection 10.5 Early Site Closure or Trial Termination	Some differences exist in the presentation of data from Section 10 onwards: • TransCelerate places all the information in Section 10 using a series of appendices • Draft ICH M11 presents the information in separate Level 2 headings The overall information presented is generally similar between the two templates
11 General Considerations: Risk Management and Quality Assurance	No Section 11	11.1 Quality Tolerance Limits 11.2 Data Quality Assurance 11.3 Source Data	TransCelerate places this information in Section 10.1 Appendix 1 Regulatory, Ethical, and Study Oversight Considerations (Section 10.1.8 Data Quality Assurance, Section 10.1.9 Source Documents)

Level 1 heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 heading	Draft ICH M11 Level 2 heading	Brief comment
12 Appendix: Adverse Events and Serious Adverse Events – Definitions, Severity, And Causality	No Section 12	12.1 Further Details and Clarifications on the AE Definition 12.2 Further Details and Clarifications on the SAE Definition 12.3 Severity 12.4 Causality	In TransCelerate CPT these sections are addressed in: 10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting
13 Appendix: Definitions and Supporting Operational Details	No Section 13	13.1 Contraception and Pregnancy Testing 13.2 Clinical Laboratory Tests 13.3 Country/Region-Specific Differences 13.4 Prior Protocol Amendments	In TransCelerate CPT these sections are addressed in: 10.2. Appendix 2: Clinical Laboratory Tests 10.4. Appendix 4: Contraceptive and Barrier Guidance 10.8. Appendix 8: Country-specific Requirements 10.9 Appendix 9: Protocol Amendment History
14 Appendix: Glossary of Terms	No Section 14	Define abbreviations and other terms used in the protocol	In TransCelerate CPT this section is presented immediately after the TOC at the front of the document
15 Appendix: References	References are in Section 11	15 Appendix: References	

Abbreviations: CPT= Common Protocol template; SoA= Schedule of Activities

(https://www.imi.europa.eu/projects-results/ project-factsheets/eu-pearl). Knowing that ICH trumps everything, we expect the structure of the clinical trial protocol will be set by the final ICH M11 guidance when it is eventually issued. TransCelerate will wait until ICH M11 is more mature before they comment further. Meanwhile, on December 13, 2022, the **CORE Reference Project Team** published an **open-access** resource titled "**TransCelerate CPT (v009) Versus Draft ICH M11 Template: A Comparison of Level 2 Headings**" to support familiarisation with ICH M11. This resource is available at https://www.core-reference.org/news-summaries/core-reference-project-team-compare-transcelerate-cpt-v009-and-draft-ich-m11-step-2-templates-a-comparison-of-level-2-headings/ and is replicated in Table 1.

It is appropriate in this "Clinical Trials" themed issue of MEW that we hear from Zuo Yen Lee – an experienced medical writer at a global CRO that serves biotechnology companies – about the complexities of oncology design and bias avoidance. Her article, "To bias or not to bias in oncology clinical trials: Perspectives on design, endpoint selection, and reporting", begins on p. 46. As ICH M11 matures, we will undoubtedly see its impact on a range of study designs, including oncology trials.

CORE Reference Project

In November 2022, the CORE Reference Project Team released an animation: https://youtu.be/ANCvoWBULb8 and https://www.core-reference.org. We did this to showcase and promote awareness of this open access resource to those new to our profession. We also have a landing page on the EMWA website (https://www.emwa.org/resources/ core-reference/) that provides the links that underpin the resources. Also in the offing is a planned CORE Reference website overhaul in late 2023/early 2024 that will produce a cleaner, slicker website to improve your visitor experience.

The CORE Reference Team will also be hosting an open introductory and Q&A session on CORE Reference and the CPD resources during the EMWA May 2023 conference in Prague, so do please come and meet us on Friday May 12, 2023, at 17.15-18.15. In June 2023, we plan an online open session on the resources and also featuring T&D in Asia.

Don't forget that you can receive CPD resources direct to your inbox (sign up at: https://www.core-reference.org/subscribe), or you may wish to periodically check the News Summary page of the existing website (https://www.core-reference.org/news-summaries/) where information gathered on matters concerning RPD and clinical study reporting is archived monthly. A selection of the most relevant information in the world of RPD in the last few months is in Table 2. Enjoy!

Table 2. Selected regulatory information shared via CORE Reference (September 2022 – December 2022)

Disseminated information	Brief description	Link
September 2022 Highlights		
Final FDA guidance: "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products"	Encourages sponsors to identify in their submission certain uses of RWD/RWE. Also applies to submissions for investigational new drug applications, new drug applications, and biologics license applications that contain RWD/RWE intended to support a regulatory decision regarding product safety and/or effectiveness	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drug-and-biological-products?utm_medium=email&utm_source=govdelivery
TransCelerate and Association of Clinical Research Organizations Member Companies: Points to consider	Points to consider when developing a CSR which has interruptions due to unforeseen circumstances e.g., war, a pandemic or other public health emergency, or any geospatial disruption.	https://www.transceleratebiopharmainc.com/wp-content/uploads/2022/09/ACRO-TC-CSR-Statement-9.12.22-FINAL-for-posting-1.pdf
NIH Plain Language Checklist for Lay Brief Summaries	Checklist refers to plain language best practices to help investigators write brief summaries of clinical trials that can be easily understood by the general public	https://prsinfo.clinicaltrials.gov/Plain_Language_Checklist_for_Lay_Brief_Summaries.pdf?utm_medium=email&utm_source=govdelivery
Canadian Institute of Health Research Policy Guide	Clinical trials must be registered and results published within the mandated time frame in order to remain eligible for any new funding	https://cihr-irsc.gc.ca/e/52820.html
Good Publication Practice (GPP) Guidelines for Company-Sponsored Biomedical Research: 2022 Update	Update to the GPP guidelines	https://doi.org/10.7326/M22-1460
October 2022 Highlights		
FDA final guidance entitled "Multiple Endpoints in Clinical Trials Guidance for Industry"	Describes various strategies for grouping and ordering endpoints for analysis and applying some well-recognised statistical methods for managing multiplicity within a study in order to control the chance of making erroneous conclusions about a drug's effects. The final guidance also incorporates a reference to the International Council for Harmonization's (ICH) E9(R1) guideline on estimands and how these fit into primary and secondary endpoint families.	https://www.fda.gov/media/162416/download
BMJ open access paper	Describes novel issues specific to the registration and reporting of results for master protocols and proposes an approach to support transparent, complete, and timely reporting to trial registries and results databases such as ClinicalTrials.gov. The process has the potential to be applied broadly to other trial registries and results databases.	https://doi.org/10.1136/bmj-2021-067745
Publication asking: "Is Intention to Treat Still the Gold Standard or Should Health Technology Assessment Agencies Embrace a Broader Estimands Framework?"	Insights and perspectives from the National Institute for Health and Care Excellence and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E9 (R1) Addendum	https://doi.org/10.1016/j.jval.2022.08.008

Disseminated information	Brief description	Link
ICH released a Step 2 draft guideline (ICH M11) outlining a harmonised template for clinical trial protocols to support consistent reporting among sponsors.	The draft guideline, plus template and template technical specifications, were released for public consultation. The scope of ICH M11 is to establish common instructions for placement of content and information on technical attributes.	Link to draft guideline: https://database.ich.org/sites/default/files/ICH_M11_draft_Guideline_Step2_2022_0904.pdf Link to template https://database.ich.org/sites/default/files/ICH_M11_Template_Step2_2022_0904.pdf
November 2022 Highlights		
EMA – guidance to companies on the retention/removal of Protected Personal Data and identification of Commercially Confidential Information during the preparation of Risk Management Plans (RMPs).	Contains changes of editorial nature that should be implemented in the RMP during the scientific review process prior to the opinion and adoption of the final RMP version.	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-anonymisation-protected-personal-data-assessment-commercially-confidential-information_en.pdf
TransCelerate released Clinical Template Suite (CTS) Release Addendum	This is a track changes clinical protocol template (CPT v009) with limited updates. The addendum also explains that the next round of templates will be released after June 2023, in order to allow alignment with ICH M11 and EU Patient Centric Clinical Trial Platforms	https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/
EMA released the updated (Rev. 14) "Guidance for Applicants seeking scientific advice and protocol assistance".	Update clarifies the scope and nature of scientific advice and protocol assistance, such as requests for paediatric development, structure/content of the briefing package, and the procedure for fee determination and payment. The major changes to the document are for clarity and conciseness	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf
CTIS online training modules updates	• CTIS Evaluation Timelines – overview of timelines and deadlines for tasks and actions across the Clinical Trial Application process. • Management of Roles and Permissions – step by step guide on how to request the high-level administrator role for CTIS. • FAQs - Management of Roles and Permissions – answers to questions regarding basic principles to access CTIS for the first time, roles and permissions, CTIS user management approaches, user profile management and the main user groups.	• https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-evaluation-timelines_en.pdf • https://www.ema.europa.eu/en/documents/other/step-step-guide-high-level-ctis-administrator-management-roles-permissions-ctis-training-programme_en.pdf • https://www.ema.europa.eu/en/documents/other/faqs-management-roles-permissions-ctis-training-programme-module-07_en.pdf

Abbreviations - CTIS: Clinical Trials Information System; GPP: Good Publication Practice; RMP: Risk Management Plan(s); RWD: Real-World Data; RWE: Real-World Evidence

Sign up to CORE Reference using this link: https://www.core-reference.org/subscribe to receive the regular, real time email updates in full, with current information on regulatory reporting and public disclosure which support the continuing professional development (CPD) needs of medical and regulatory writers. The topics covered in the more extensive email updates include FDA and EMA guidance and news, real-world data, transparency and disclosure resources and news, development strategy news, news from Asia regulators, and regulatory guidances open for public consultation. The emailed information is collated monthly and archived here: https://www.core-reference.org/news-summaries/

In the Bookstores

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Medical writing books on a budget

Over the years, I have accumulated several shelves of books relating to medical writing. All were chosen because they provide insight into medical writing techniques, useful guidance on style and grammar, or enhance my understanding of other related subjects (e.g. statistics). On the whole, the contents of the books have remained pertinent and I return to them again and again.

Educational books can be expensive but the availability of ebook versions can result in a reduced cost. I have therefore searched Amazon UK to compile a list of ebooks that were easily accessible, not too expensive (i.e., cost less than £10), and might help enhance your medical writing. For some ebooks, if you have Kindle unlimited there is no charge to download. I have not included any regulatory guidance books since they usually only provide a snapshot of regulations and information can become quickly outdated.

I declare that this list of Medical Writing Books on a Budget (Table 1) was not prepared as a systematic review of available books, hence you and I must accept that there is inherent bias.

My criteria for compiling the list were:

1. A version of the book should cost less than £10 (approximately 10 Euros)
2. There should be an English language version
3. The book did not cover regulatory medical writing
4. I reviewed the available information and decided the book might inform your medical writing.

My search was carried out on Amazon UK and last compiled on November 15, 2022. The star rating for each book is given by customers on Amazon. Where a paperback version also met the criteria for price this information is included.

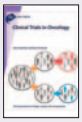
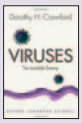
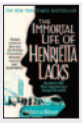
For information, *Bad Pharma* and *The Immortal Life of Henrietta Lacks* were both previously reviewed by an EMWA member for this section. I have included *Lucky Man: A Memoir* by Michael J. Fox to offer a patient perspective of living with disease.

There are many other books that appeared relevant and I would have liked to select – but they cost more than my set limit, hence they were excluded. I hope you find those that remain both informative and useful.

Written, reviewed and compiled by Alison McIntosh

I have therefore searched Amazon UK to compile a list of ebooks that were easily accessible, not too expensive (i.e., cost less than £10), and might help enhance your medical writing.

Table 1. Medical writing books on a budget

Book title	Author and publisher	Customer reviews	Cost
 *Effective Medical Writing: An Academic Writing Guide*	Author Thomas Buckingham Publisher: (Oct 4, 2017)	4.4 stars out of 5 (29 reviews)	Kindle edition price £6.01
 *Medical Writing: A Brief Guide for Beginners*	Author: Carol Scott-Conner Publisher: Rachel Lord Press (Oct 23, 2015)	3.5 stars out of 5 (3 reviews)	Kindle edition price £7.26
 *Writing Scientific Papers in English Successfully: Your Complete Roadmap*	Author: Ethel Schuster Editors, Haim Levkowitz, Osvaldo N. Oliveira, Jr Publisher: hyprtek.com, inc. (Nov 23, 2014)	4.7 stars out of 5 (50 reviews)	Paperback edition £7.65 Kindle edition price £7.63
 *Fast Facts: Clinical Trials in Oncology The Fundamentals of Design, Conduct and Interpretation*	Author: A Hackshaw, G.C.E. Stuart Publisher: S. Karger; 1st edition (Dec 18, 2020)	5 stars out of 5 (3 reviews)	Free in Kindle Store
 *Eats, Shoots and Leaves*	Author: Lynne Truss Publisher: Fourth Estate (May 26, 2011)	4.5 stars out of 5 (2,825 reviews)	Paperback edition £4.83 Kindle edition price £3.99
 *Oxford Guide to Plain English*	Author: Martin Cutts Publisher: Oxford University Press; (Feb 27, 2020)	4.6 stars out of 5 (155 reviews)	Paperback edition £7.15 Kindle edition price £4.72
 *The Art of Statistics: Learning from Data*	Author: David Spiegelhalter Publisher: Pelican (Feb 13, 2020)	4.5 stars out of 5 (2,865 reviews)	Kindle edition price £1.99
 *How to Make the World Add Up: Ten Rules for Thinking Differently About Numbers*	Author: Tim Harford Publisher: The Bridge Street Press (Sept 17, 2020)	4.6 stars out of 5 (1,186 reviews)	Paperback edition £5.22 Kindle edition price £0.99
 *How Charts Lie: Getting Smarter about Visual Information*	Author: Alberto Cairo Publisher: W. W. Norton & Company (Oct 15, 2019)	4.7 stars out of 5 (348 reviews)	Kindle edition price £8.96
 *Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients**	Author: Ben Goldacre Publisher: Fourth Estate (Sept 25, 2012)	4.5 stars out of 5 (953 reviews)	Paperback edition £8.49 Kindle edition price £3.99
 *Viruses: The Invisible Enemy (Oxford Landmark Science)*	Author: Dorothy H Crawford OUP Oxford; 2nd edition (Nov 5, 2021)	4.6 stars out of 5 (19 reviews)	Paperback edition £7.99 Kindle edition price £5.57
 *The Immortal Life of Henrietta Lacks**	Author: Rebecca Skloot Publisher: Picador (June 3, 2010)	4.6 stars out of 5 (15,305 reviews)	Paperback edition £8.38 Kindle edition price £4.99
 *Lucky Man: A Memoir*	Author: Michael J Fox Publisher: Ebury Press; 1st Paperback Edition (Jan 2, 2003)	4.6 stars out of 5 (1,886 reviews)	Kindle edition price £9.49

* Previously reviewed by an EMWA member for In the BookstoresLast updated on Oct 6, 2022

Veterinary Medical Writing

SECTION EDITOR

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Editorial

There have been countless columns written about "herd immunity" during and since the COVID-19 pandemic. But what does it take to write about a real-life herd? As in a herd of domestic cattle, sheep, llama or buffalo? Or even a flock of chickens, turkeys or geese? Would you be confident writing medical content for these production animal species? In this issue of Veterinary Medical Writing, large-animal-veterinarian-turned medical writer Rhona Fraser draws on her experience as a dairy practitioner in New Zealand. In her article, Rhona highlights the aspects of production animal health that are different from those of human and companion animal practice that should be reflected in all medical communications based on these species. A perhaps unpalatable truth, however, is that production animal diseases must be considered for their economic impact as well as the individual's well-being. In addition, there are essential additional regulatory aspects of food safety and animal welfare. Finally, the close association of, for example, cattle with their environment has always been appreciated by large animal veterinarians in a way which has eluded their human- and companion-animal counterparts. One could say that they are the original One Health practitioners. After a brief hiatus, From the Horses' Mouth returns for 2023. Featured in this issue is a report on the first data published from the RECOVER database, which suggests there is more to be learnt about the outcomes of cats and dogs for cardiopulmonary resuscitation. Also revealed are details of a gem of a One Health podcast.

Louisa Marcombes

Welly boots and spreadsheets: A rough guide to production animal medicine for medical writers

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How does veterinary medical writing differ from human medical writing? Formulating an answer to this question is a core preoccupation of EMWA's Veterinary Medical Writing – Special Interest Group. Companion animal medicine and human medicine may be inherently different. However, the fundamental principles of successful clinical case management are similar:[1] The focus is on the individual, whether the patient is human or veterinary. In contrast, we frame clinical production animal health, a term that refers to species such as cattle, sheep, swine, and poultry, in the context of the herd. Economic considerations, welfare concerns, environmental impacts, and additional regulatory requirements must all be considered alongside the health of the individual production animal. As a result, the role of the production animal veterinarian has evolved profoundly over the past few decades from the welly-wearing James Herriot stereotype to a position more reminiscent of the business consultant.[2] They still wear the wellies, but the modern dairy vet's involvement on the farm goes beyond the clinical, with knowledge transfer and consultancy at the fore and a proactive approach promoting disease prevention.[3] Here, I have drawn on my own experience as a dairy veterinarian in New Zealand to highlight the unique aspects of production animal health that medical writers should be aware of. Although I focus on dairy practice in this article, many of the principles described here apply to global best practices in the beef, swine, lamb, and poultry industries.

> Knowledge transfer may involve workshops and tutorials at the clinic or farm.

The herd approach

Economic pressures, demographic shifts, technological innovations, and evolving regulatory frameworks have transformed the modern global dairy industry. Increasing milk production per cow and a limited supply of skilled workers heighten the need for establishing farm-specific protocols. Such systems minimise human error and ensure best practices are embedded at each dairy production site.[4] Although regularly faced with the individual sick animal, this often indicates a more extensive underlying problem requiring a comprehensive review of husbandry practice at the herd level.[5] As production diseases are multifactorial and often directly related to the production process, the dairy vet will analyse management aspects such as nutrition, the environment, and housing in parallel with clinical information. Monitoring and early diagnostic warning systems on farms – a micro version of disease surveillance in large human populations – are essential tools for problem analysis and facilitating a proactive early intervention and prevention approach.[5] The farm vet systematically interprets production data, reviews feed rations calculations, and provides an overall assessment of herd health status.[6] The data collected informs a comprehensive whole herd approach, includes nutritional advice, reproductive analysis and management, milk quality management, and consultancy planning, and requires an understanding of the farm at an operational level.[7]

Communication

Communication in small animal medicine follows a similar consultative approach to human medicine: gathering history, examining the patient, and producing and carrying out a treatment plan.

It is a problem-orientated approach. Although the management of the individual sick farm animal follows a similar structure, the communication process is more solution-focused, addressing underlying issues to improve the overall performance of the farm.[5] This is a longer-term procedure centred on defining, prioritising,

and agreeing on goals with the producer. Excellent, clear communication fostering a partnership between the veterinarian and the farmer is central to achieving the mutual trust and understanding necessary to achieve these goals.[2] Furthermore, educating farmers is critical to a successful client relationship and achieving improved herd health and welfare goals.[8] Vets seldom lack clinical veterinary knowledge; the challenge for the dairy veterinarian is ensuring excellent communication with farm staff.[8]

Knowledge transfer may involve workshops and tutorials at the clinic or farm. Standard operating procedures tailored for the individual farm systemise farm practices ensuring consistent, evidence-based husbandry. Successful engagement, rewarding relationships and optimal animal health and welfare outcomes happen when vets take this farmer-centred approach. Understanding the client's unique circumstances and priorities and promptly communicating clearly with plain language improves client satisfaction and, most importantly, engagement.

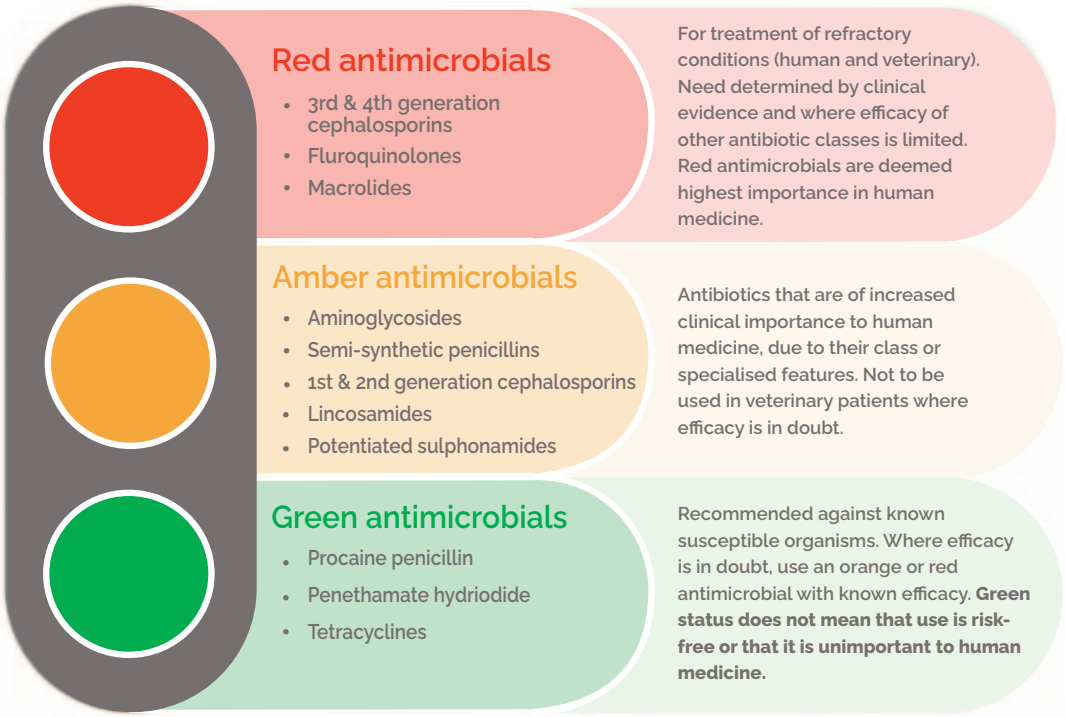

Figure 1. The "traffic light" guidance for antimicrobial use in veterinary patients, adapted from the New Zealand Veterinary Association prescribing guidelines. Antimicrobials are classified according to their importance to human medicine in the face on antimicrobial resistance.

Adapted from the New Zealand Veterinary Association. Reproduced with permission.

Prescribing for farmers

The use of on-farm antimicrobials is a good example. Antimicrobials are essential in treating, preventing, and controlling food-animal diseases. In New Zealand, prescribing antimicrobials is regulated by the Agricultural Compounds and Veterinary Medicines Act.[9] You must have a bona fide veterinarian-client relationship to prescribe restricted veterinary medicines, such as antibiotics. This means visiting the farm at least once a year, although most farmers have more frequent visits. Veterinarians undertake an annual consult with their clients to decide on an allowance of restricted veterinary medicines (RVM) available for the season and to ensure farm staff understand drug classes and uses.[10]

We discuss common conditions on farms, such as mastitis, metritis, and lameness. Together we determine treatment strategies and estimate the amount of medication required based on the farm's history. In practice, this allows farmers to keep a stock of medicines on the farm to use for immediate treatment of common conditions as required. The annual RVM consultation provides access to the agreed allotment of medicines throughout the year. The only exception is "red" antibiotics (see below), for which access must be reviewed every four months. In my experience, this discourages the use of these critically important antibiotics. When conducted comprehensively, the RVM discussion educates farmers on the effective and responsible use of medicines. As inappropriate treatments are often unsuccessful and expensive, I have found farmers to be receptive to such discussions, providing an open and collaborative approach is taken by the vet. Dairy veterinarians are inherently available to farmers – when they encounter a scenario outside our discussions, farmers mostly call to confirm an appropriate treatment strategy. This may not happen in every client-vet relationship, but it is possible. Through education, our farmers adopt an evidence-based, informed approach in collaboration with their trusted advisor rather than indiscriminately reaching for antibiotics. It is important to remember that although vets possess expert clinical knowledge, farmers have specialist knowledge of their farm's systems. Thus, the veterinarian's style and manner of approach to these conversations determine the likelihood of a successful outcome.

The Antimicrobial Strategic Group of the New Zealand Veterinary Association (NZVA) produced guidelines to help direct veterinarians on the judicious use of antibiotics. A traffic light system for guiding prescribing was created based on the WHO classification of first (green) and second (amber) line antibiotics followed by "red" antibiotics(11), which are considered critically important and used in treating refractory conditions in human and veterinary medicine. A summary of the types of antibiotics listed at each level is provided in Figure 1. We utilise the traffic light system during RVM consults to advise treatment plans for common conditions the farmer encounters. Routine use of red antibiotics, such as third-generation cephalosporins, is discouraged – these prescriptions must be reviewed every four months.

The Dairy Antibiogram (DAB) contributes to ethical product stewardship by monitoring antibiotic effectiveness on common mastitis pathogens in bulk milk samples. The DAB utilises an advanced screening tool called broth microdilution, a quantitative test, to define the minimum inhibitory concentration. Previously agar disc diffusion assays were used to determine antibiotic sensitivities. However, they have significant limitations and require care with interpretation.[12] In addition, we can build a database with this DAB, so antimicrobial use

patterns and their effects on resistance can be monitored and investigated. They can determine the "wild type" population from the "non-wild" type using epidemiological cut-off values, thus detecting the emergence of antimicrobial-resistant phenotypes. I have found the DAB to be an indispensable tool for evidence-based guidance on prescribing antibiotics. Dairy vets strive to lead the way with prudent antimicrobial use. Recent reports from the EMA indicate that sales of antibiotics for animal use have almost halved between 2011 and 2021.[13]

Historically antibiotics were used as growth promoters in livestock. Europe and New Zealand banned this practice following public pressure in 2006[14] and 2002,[15] respectively. However, outlawing this practice resulted in an increased requirement for therapeutic antibiotics despite improvements in husbandry. Unfortunately, these therapeutic antibiotics had more overlap with those used in human medicine.[16]

Antibiotic medications are also a critical global resource, with antimicrobial resistance recognised as one of the most severe public health threats.[17,18] On January 28, 2022, the EU enforced new veterinary medicine regulations (veterinary medicines Regulation EU 2019/6 and medicated feed EU 2019/4), aiming to reinforce responsible antibiotic use.[19] In parallel with this, the New Zealand Veterinary Association declared an ambitious goal: By 2030, New Zealand will not need antimicrobials to maintain animal health and wellness.[20] New Zealand ranks as the third lowest consumer of antimicrobials globally, behind Norway and Iceland.[20] This is perhaps due to the extensive nature of their production systems. New Zealand Food Safety has reported a steady decline in antibiotic use, with sales for multi-species products decreasing by 5% from 2018 to 2019.[21] Focus on minimising dry cow therapies have yielded some significant gains, dropping antibiotic use by almost 20% over two years (2017–19).[21] Elsewhere, the latest UK Veterinary Antibiotic Resistance and Sales Surveillance data shows that sales of antibiotics for livestock use are at their lowest levels, now reduced by 55% since 2014. In addition, critically important antibiotics sales (crucial for treating human diseases) have declined by a profound 83% since 2014.[22]

Sustainability considerations and the One Health approach

Humans, animals, and the ecosystem do not exist in isolation. The health or otherwise of one group will impact the others. Therefore, it is incumbent upon production animal veterinarians to play their part in taking an integrative approach towards medicine and food safety.[16] However, a one-health approach can be challenging as veterinary, medical, and political interests are not always aligned. In addition, vets and farmers have concerns about compromising animal health and welfare through restrictions on antimicrobial use. On September 16, 2021, the European Parliament rejected a motion to increase antimicrobials restricted to human-only use. An open letter with 9,000 signatories from veterinarians and animal welfare organisations appealed against the resolution, arguing an unacceptable threat to animal welfare.[23]

> Monitoring and early diagnostic warning systems on farms – a micro version of disease surveillance in large human populations - are essential tools for problem analysis and facilitating a proactive early intervention and prevention approach.

Mastitis is a typical example of a common dairy production disease and always presents significant health, welfare, and production challenges. It is also a critical control point for organisms causing foodborne diseases in dairy products. By controlling mastitis, we can simultaneously reduce environmental contamination and improve milk quality, quantity, and human and animal health.[16] The treatment and prevention of mastitis account for approximately 85% of antimicrobial use on New Zealand farms.[24] Introducing blanket dry cow therapy (administration of intramammary antimicrobials to the whole herd at the end of the milking season) revolutionised mastitis control by curing current infections and preventing new infections in the dry period.[25] A further advance came from teat sealants and selective dry cow therapy, dramatically reducing antibiotics on farms without impacting the health and welfare of the cow or milk quality.[26]

In the global dairy industry, sustainability is increasingly taking a central role. Traditionally, producers reward farmers for the quantity and quality of milk. Standards used vary by geographic region: European producers receive a premium for milk volume in Europe, whereas New Zealand dairy farmers receive compensation for milk protein and fat content. In addition, all farmers incur bonuses or penalties for hygiene and animal health parameters.[27] However, the trend is for

dairy companies to introduce sustainability incentives. New Zealand's dairy co-operative, Fonterra, is a company owned by the farmers who supply it and membership improves the economic return of the individual. They launched The Cooperative Difference in 2019 – a holistic framework for looking after people, animals, the environment, and the co-op itself.[28] The base level, Te Pūtake, requires farms to complete an Animal Wellbeing Plan (in consultation with their vet), design an environmental plan, and meet all expectations of being a good employer. On completion, they may progress to Te Puku – awarded for maintaining milk quality excellence for at least 30 days of the season. Te Tihi is a recognition award for top performers from Fonterra, celebrating suppliers delivering excellent milk quality for over 90% of the season.[28]

Arla Foods introduced a similar sustainability incentive in Europe. This has proved to be highly successful, with around 95% of their farmers signing up for this voluntary rewards system[29] and engaging in more sustainable farm practices. This future-focused system sees farmers rewarded for performing well in areas like feed efficiency, fertiliser use, land use, protein efficiency and animal robustness – which refers to animal health and is measured by cow mortality percentage rates.[30]

Another crucial component of sustainable dairying is efficient heifer rearing. Vets focus on enabling farmers to reach the target of rearing a fully grown healthy heifer, capable of delivering their first calf without complications at 23 months.[31] Losing production efficiency contributes to waste and poor sustainability in dairy practices.

Regulatory considerations

Medicating farm animals is usually by injection, in water, or feed preparations. Doses are calculated on a body weight basis, requiring accurate estimations to ensure correct dosing.[20] For food-producing animals, preventing pharmaceutical residues from entering the food chain is of critical importance. After treatment, a significant proportion of antibiotics remain unchanged or are excreted as active metabolites (17% – 90%),[31] so livestock manure from treated animals has the potential to contaminate the environment. This contamination not only deteriorates the water quality but also impacts all trophic levels, from soil microbes to plants and food production. Therefore, food safety and milk quality begin on-farm. To avoid harmful residues in food products, all medications for food-producing animals must have defined withdrawal times,[32] within which agricultural produce must not enter the food chain. Residues can enter the milk supply through failure to withhold milk for the appropriate amount of time or contaminated feed.

In the case of antibiotics, the main consequence of antibacterial residues entering the food chain is its effect on the human gut microbiome, which is pivotal in determining health status and can be negatively affected by these antibiotic residues.[16] Studies suggest an imbalance of the microbiome may allow the proliferation of harmful bacteria and health issues such as colitis, intestinal disorders, and colorectal cancer.[33] To safeguard against any failure of on-farm protective measures, dairy companies implement an additional level of residue management through screening and pasteurisation.[34] In addition, there are various third-party quality assurance services. For example, in New Zealand, the Ministry for Primary Industries runs the National Chemical Contaminants Programme, testing milk and dairy products to ensure that residues and contaminant levels fall within acceptable standards. However, more work is needed to understand how pharmaceutical residues impact human, veterinary, and environmental health.

Medical writing for production animals

In many ways, the medical writing based on a dog with mastitis – drug licensing, drug safety, clinician education, patient or client information – is equivalent to that of a human patient with mastitis. For the bovine patient with mastitis who is part of a food production system, however, medical communications require keeping the context of the commercial value of the patient and the health impact at a herd level. Vets and farmers must also consider specific regulatory and welfare considerations. Furthermore, in common with companion animals, the evidence derived from production animal studies is often degraded by poor study design and reporting.[35,36] However, interestingly, in some fields, such as reproduction, a higher proportion of studies in dairy cattle (33% of articles reviewed) are of sufficient quality to draw sound conclusions than comparable studies in canine (7%) or equine reproduction (11%).[37]

In summary, the global dairy industry has evolved and will continue as a One Health approach becomes the orthodoxy. Establishing solid relationships with clients and understanding their unique goals and challenges – effecting a "precision" herd medicine approach – is paramount for shaping sustainable change on the farm necessary to ensure global food security. An empathetic approach to educating all stakeholders is key to this success. Open collaboration between industries can benefit animals, humans, and the environment. This should be our collective goal.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by her employer or EMWA.

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References

1. Ritter C, Adams CL, Kelton DF, Barkema HW. Factors associated with dairy farmers' satisfaction and preparedness to adopt recommendations after veterinary herd health visits. J Dairy Sci. 2019;102(5):4280–93.
2. Ritter C, Adams CL, Kelton DF, Barkema HW. Clinical communication patterns of veterinary practitioners during dairy herd health and production management farm visits. J Dairy Sci. 2018;101(11):10337–50.

3. Skjølstrup NK, Nielsen LR, Jensen CS, Lastein DB. Veterinary herd health consultancy and antimicrobial use in dairy herds. Front Vet Sci. 2021 ;7:547975.2015;
4. Barkema HW, von Keyserlingk MAG, Kastelic JP, et al. Invited review: Changes in the dairy industry affecting dairy cattle health and welfare. J Dairy Sci. 2015;98(11):7426–45.
5. Kleen JL, Atkinson O, Noordhuizen JPTM. Communication in production animal medicine: Modelling a complex interaction with the example of dairy herd health medicine. Irish Vet J. 2011;64:8
6. LeBlanc SJ, Lissemore KD, Kelton DF, et al. Major advances in disease prevention in dairy cattle. J Dairy Sci.2006;89(4): 1267–79.
7. da Silva JC, Noordhuizen JPTM, Vagneur M, Bexiga R, et al. Veterinary dairy herd health management in Europe Constraints and perspectives. Vet Q. 2006 Mar;28(1):23–32.
8. Bard AM, Main D, Roe E, et al. To change or not to change? Veterinarian and farmer perceptions of relational factors influencing the enactment of veterinary advice on dairy farms in the United Kingdom. J Dairy Sci. 2019;102(11):10379–94.
9. McDougall S, Compton C, Botha N. Factors influencing antimicrobial prescribing by veterinarians and usage by dairy farmers in New Zealand. N Z Vet J. 2017;65(2):84–92.
10. Industries M for P. Selling restricted veterinary medicines (RVMs) under the ACVM Act 1997 | MPI–Ministry for Primary Industries. A New Zealand Government Department. Ministry for Primary Industries; [cited 2022 Dec 9]. Available from: https://www.mpi.govt.nz/animals/veterinary-medicines-acvm/selling-veterinary-medicines/restricted-veterinary-medicine-sellers/
11. Antimicrobial resistance (AMR). New Zealand Veterinary Association [cited 2022 Dec 9]. Available from: https://nzva.org.nz/resource/general/amr/
12. Gibson I. Oxacillin (cloxacillin) resistance of major mastitis pathogens in New Zealand. Vetscript. 2010;23(4):37.
13. EMA. Sales of antibiotics for animal use have almost halved between 2011–2021 [cited 2022 Dec 9]. Available from: https://fve.org/publications/antimicrobial-use-in-animals-in-the-eu-almost-halved-in-last-10-years-due-to-strong-commitment-of-the-animal-health-sector/
14. Ban on antibiotics as growth promoters in animal feed enters into effect. European Commission. 2005 [cited 2023 Jan 4]. Available from: https://ec.europa.eu/commission/presscorner/detail/en/IP_05_1687
15. Hormonal Growth Promotant and Antibiotic use in New Zealand Cattle Hormonal Growth Promotants [cited January 4, 2023]. Available from: https://www.waitakibio.com/wp-content/uploads/2016/04/hormone-growth-promotant-and-antibiotic-use.pdf
16. Garcia SN, Osburn BI, Cullor JS. A one health perspective on dairy production and dairy food safety. One Health. 2019;7:100086.
17. Tiseo K, Huber L, Gilbert M, et al. Global trends in antimicrobial use in food animals from 2017 to 2030. Antibiotics. 2020;9(12):918.
18. Burnside E. The first veterinary EMWA workshop: A witness statement. Med Writ. 2022;31(2):111–15.
19. EMA. Veterinary Medicinal Products Regulation. 2019 [cited December 9, 2022]. Available from: https://www.ema.europa.eu/en/veterinary-regulatory/overview/veterinary-medicinal-products-regulation
20. Hillerton J, Bryan M, Beattie B, et al. Use of antimicrobials for food animals in New Zealand: Updated estimates to identify a baseline to measure targeted reductions. N Z Vet J. 2021;69(3):180–5.
21. 2019 Antibiotic Agricultural Compound Sales Analysis Prepared for the Assurance Directorate by the Agricultural Compounds and Veterinary Medicines team. 2021 [cited December 8, 2022]. Available from: https://www.mpi.govt.nz/dmsdocument/48622/direct
22. Webb A. Food production antibiotic sales drop to record low. Vet Times. 2022. Available from: https://www.vettimes.co.uk/news/food-production-antibiotic-sales-drop-to-record-low/
23. Marcombes L, Bell J, Smith H. From the horse's mouth. Veterinary Medical Writing. Med Writ. 2021;30:60–3.
24. Pattis I, Weaver L, Burgess S, et al. Antimicrobial resistance in New Zealand – A One Health perspective. Antibiotics. 2022;11(6):778.
25. Ruegg PL. A 100-year review: Mastitis detection, management, and prevention. J Dairy Sci. 2017;100(12):10381–97.
26. Mcdougall S, Cuttance E, O'Sullivan M, et al. Predicting infection status at drying off, and the efficacy of internal teat sealants in dairy cows. Proceedings of the Society of Dairy Cattle Veterinarians of the New Zealand Veterinary Association. 2017: 35–8.
27. Bailey AP, Garforth C. An industry viewpoint on the role of farm assurance in delivering food safety to the consumer: The case of the dairy sector of England and Wales. Food Policy. 2014;45:14–24.

28. Together we make the difference. Fonterra [cited 2023 Jan 4]. Available from: https://www.fonterra.com/nz/en/campaign/make-the-difference.html
29. dairyreporter.com. Arla's sustainability incentive explained: How farmers can earn extra eurocents for their milk [cited 2023 Jan 4]. Available from: https://www.dairyreporter.com/Article/2022/10/11/Arla-s-Sustainability-Incentive-explained-How-dairy-farmers-can-earn-extra-eurocents-for-their-milk
30. How climate checks are driving action to reduce emissions on Aria farms [cited December 28 2022]. Available from: https://cdb.arla.com/api/assets/arla-uk/b42024a3-cd61-4948-a8ae-c678cfa93b6a/climate-check-report-2022-final300922pdf-1-.pdf/
31. An introduction to sustainability. Vet Sustain [cited 2022 Dec 9]. Available from: https://vetsustain.org/resources/into-to-sustainability-farm-practice.
32. Begemann S, Watkins F, Van Hoyweghen I, et al. The governance of UK dairy antibiotic use: Industry-led policy in action. Front Vet Sci. [cited 2022 Dec 8]. Available from: https://www.frontiersin.org/articles/10.3389/fvets.2020.00557
33. Ben Y, Fu C, Hu M, et al. Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: A review. Env Res. 2019;169:483–93.
34. Redding LE, Parsons B, Bender JS. Educational interventions to address misconceptions about antibiotic residues in milk can alter consumer perceptions and may affect purchasing habits. J Dairy Sci. 2021;104(11):11474–85.
35. Dean RS. Veterinary clinical trials are on trial. Vet Rec. 2017;181(8):193–4
36. Schulte E, Arlt SP. Study design quality of research in dogs published in peer-reviewed journals. Vet Rec. 2022;e1382.
37. Simoneit C, Heuwieser W, Arlt S. Evidence-based medicine in bovine, equine and canine reproduction: quality of the current literature. Theriogenology. 2011;76: 1042–50.

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Rhona Fraser, BSc, BVMS, Freelance Medical and Veterinary Writer, originally from Scotland, has spent the last decade living in New Zealand. Educating and collaborating with farmers has always been her passion. After 19 years, she's swapped the field for a desk and transferred this enthusiasm to the realm of medical writing.

From the Horse's Mouth

The quarterly pick of the news from the veterinary world

The first data on small animal cardiopulmonary resuscitation (CPR) outcomes from the RECOVERY registry was published in the December 2022 issue of *The Journal of Veterinary Emergency and Critical Care*, as reported by vetlit.org. The RECOVER registry is an online medical database created for the standardised collection of outcomes of cats and dogs undergoing CPR in participating veterinary practices and hospitals. The registry is run by the RECOVER initiative (recoverinitiative.org), the organisation responsible for developing the pioneering RECOVER guidelines published in 2012. The guidelines are designed for use by the veterinary team to prepare for and manage cardiopulmonary arrest in their feline or canine patients and are an early example of evidence-based clinical guidelines in the veterinary field. Based on CPR events recorded on the registry between February 2016 and November 2021, this study found that from over 700 CPR events, only 3% of dogs and 2% of cats survived until hospital discharge. This compares to 7% to 8% of human patients. The authors highlighted the need for further studies to understand better the factors associated with favourable outcomes.

In January 6, 2023, the *Veterinary Times* reported on the first figures that indicate the preliminary effects of the cost-of-living crisis in the UK on pets, pet owners, and veterinarians. Their article, which detailed a recent survey by the Dogs' Trust, reported that the charity had received 50,000 calls from owners wanting to relinquish their pets in 2022. Furthermore, they also surveyed 4,000 members of the UK public. A third of respondents who were dog owners reported that they were worried about their ability to care for their pets due to rising prices, with veterinary costs being the most common concern, as stated by 46% of respondents, followed by the cost of pet food (18%). Against a rate of inflation of 10.7% in the UK in November 2022, 3% of owners reported they would consider rehoming their pets if costs continued to rise, which could eventually result in as many as 350,000 dogs needing new homes. However, with 62% of non-dog-owning respondents reporting that the current economic situation would "definitely" or "probably" stop them from acquiring a dog in 2023, the challenge of rehoming these relinquished pets could be substantial. In response to the pressures experienced by owners due to the rise in the cost of living, the Dog's Trust has opened six temporary canine food banks at a selection of their 21 rehoming centres in the UK.

If one of your new year's resolutions was to find an informative podcast or two, you could do worse than checking out this podcast from the *Humanimal Hub,* the Humanimal Connection. The first series, which comprises seven half-hour-long episodes, was launched in June 2022 and covered a diverse range of topics. From discussing the techniques adopted from human medicine to treat gunshot injuries in wild South African rhinos to lessons that human vaccine technology can learn from the veterinary sector in the wake of the COVID-19 pandemic. Make sure you catch up on season 1 before season 2 launches in 2023, which Humanimal hub Chair of trustees Professor Roberto La Ragione promises will have a very different feel.

Lingua Franca and Beyond

British or American English – Should we be bothered?

We all know that while writing any text, keeping spelling consistent – British or American English – is important. Often, we are frustrated by challenges related to ensuring consistency, particularly when clients cannot make up their mind in which English version they want their documents written. Some of us recall bitter feelings while searching for language information in poorly written instructions for authors or trying to understand preferences for regulatory documents. Should we be bothered? What is behind the differences?

Leaving aside medical writing requirements, have we ever thought that the spelling differences between British and American English reflect the historical flow of human migration, and political and cultural influences? As every other language, English has changed over the centuries and has been influenced by different languages, such as: Latin, Greek, Arabic, German and above all French. It all started with the Norman invasion in 1066 when William the Conqueror took over England and became king. He introduced French, or more precisely the Norman language, as the official language not only for authorities such as the Anglo-Norman court and the government but also for literature. It lasted for almost 300 years, until 1349 when the University of Oxford changed their teaching language from French or Latin to English. These 300 years had a very strong impact on the English that we know today. According to different sources, one-third to two-thirds of English words are of French origin.[1] However, perhaps we should consider not only the origin of words but also the way that they are spelled, for example: *queen*, *ship* and *should* according to Old English should be spelled *cwen*, *scip* and *scolde*.[2] Getting into British–American spelling differences, words such as the British *colour* and *humour* were adopted from Old French and then their spelling was simplified by Americans, and they became *color* and *humor*. Christa Bedwin will tell you more about these differences – understanding of which will make our lives as medical writers easier. Christa has been writing, editing, and teaching writing with scientists, engineers, and textbook publishers since 1997, and internationally since 2012. She grew up in the Canadian Rocky Mountains on a cattle ranch before travelling and living in different parts of the world. She also writes novels, teaches yoga, and loves sustainable organic farm volunteering in Europe.

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References

1. Wikipedia. Influence of French on English [cited on 2023 Jan 2]. Available from: https://en.wikipedia.org/wiki/Influence_of_French_on_English
2. Government of Canada. Four ways French has influenced the English language [cited 2023 Jan 2]. Available from: https://www.noslangues-ourlanguages.gc.ca/en/blogue-blog/influences-du-francais-ways-french-influenced-eng

British, American, Canadian, and Australian spelling

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"If the English language made any sense, a catastrophe would be an apostrophe with fur."
– cartoonist Doug Larson

European, Canadian, Indian, African, and Australian English normally mostly follow British spelling, with some national and regional variations. This group of Englishes is known as Commonwealth English. You might sometimes want to submit papers to American journals, however, and that means using American English spelling.

Why and how is American spelling different?

The answer is actually more scientific than you might assume. When Americans started their country and decided on their own spelling, they decided to try to make it more sensible and scientific. Remember, this was the period of history when revolution, optimisation, industrialisation, and efficiency were the prime ideas in society.

In a nutshell, British English spelling results from the polyglot experience of an indigenous language being revised, superseded, changed, and added to by many invaders over the centuries, for example: Picts, Celts, Gauls, Romans, Normans, Anglo-Saxons, Vikings. By contrast, American English seeks to make some phonetic sense of the craziness from a single industrial perspective. Just be glad they didn't go as far as they could have done. For example, we say you "bought" something, with that silent -ough, even though all you hear is "bot".

So, if you are wondering why American spelling seems to be missing some letters, now you know why: industrial efficiency!

Dictionaries

You can change your Microsoft Word dictionary to English (United Kingdom), English (Canada), English (Australia), or many other English language choices. In my current version of Word, you do this under Tools ➞ Language. If you are using a different version of Word, Google will help you solve this problem!

The most common spelling error that I have seen in scientific papers this year is for papers that are going to European sources to spell modelled and modelling with one *l*. That is the correct spelling if you are submitting to an American journal, but if you are submitting to UK, European, or Canadian sources, modelling and modelled should use *ll*, as seen in the Oxford English Dictionary, https://www.oed.com, and the many spin-off localised Oxford English Dictionaries, including the Canadian one.

If you want to spell in Australian English, use the Macquarie Dictionary: https://www.macquariedictionary.com.au

If you want to spell in American, the dictionary of choice is usually Merriam-Webster's dictionary: https://www.merriam-webster.com

Guess what the most common spelling error was that I saw in 2022 in scientific papers?

By the way, all of these dictionary pages offer amusing word games, and particularly in Macquarie's, some very entertaining and interesting articles about how words come about and other fun language topics.

I hope that answers some of your questions. I am always happy to hear from you on LinkedIn or by email.

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The author declares no conflicts of interest.

Table 1. Typical Commonwealth versus American English spelling

Type	Typical Commonwealth spelling	American spelling
Verbs ending in ise/ize	Use *ize*, so: analyze, organize, maximize/minimize **Note:** this is a modern trend. Older and more British sources may still use organise and maximise, but -ize is becoming more and more common these days.	analyze, organize, maximize/minimize
Nouns ending in our/or	Use *our*, so: colour, favourable, neighbour, labour	color, favorable, neighbor, labor
Nouns ending in re/er	Use *re*, so: centre, kilometre, but meter for an instrument such as: pH meter	center, kilometer, meter
Single *l*/double *l* in the past tense of verbs	Use *ll*, so: fuelling, modelling, modelled, travelled	fueling, modeling, modeled, traveled
Digraphs *ae* and *oe*	Use *ae* and *oe*, so: archaeology, palaeontology, oestradiol, coeliac	archeology, paleontology estradiol, celiac

Good Writing Practice

Syntactic punctuation distraction

Comma: Omission

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Introduction

Comma *omission* often occurs after a sentence-orienting syntactic unit (Examples 1, 2, and 3) and between some coordinated syntactic units (Examples 4 and 5).

After a sentence-orienting syntactic unit

Example 1: Orienting conjunctive adverb
(Introduction section: objective)
Therefore it was important to obtain normative test data for adolescents.

Revision
Therefore, it was important to obtain normative test data for adolescents.

Notes

Therefore followed by a comma (which segregates and emphasises) functions adverbially as an inter-sentence (i.e., conjunctive) marker between its sentence and the previous contiguous sentence.

Example 2: Orienting prepositional phrase
(Methods section)
For the patient group data were recorded from review (chart and x-ray), questionnaire, and neurologic tests.

Revision
For the patient group, data were recorded from review (chart and x-ray), questionnaire, and neurologic tests.

Notes

Without the comma, *data* could be misread as the object in the prepositional phrase (*for patient group data*). The prepositional phrase *for the patient group* in an orienting position avoids modifier clutter (by distancing one of the two modifiers of *were recorded*).

Example 3: Orienting adverbial clause
(Results section: preliminary interpretation)
If the data had not been analysed for heterogeneity the results would have been the same as those of previous studies.

Revision
If the data had not been analysed for heterogeneity, the results would have been the same as those of previous studies.

Notes

The punctuational demarcation of an adverb clause preceding an independent clause (a transposition from a strictly modificational position) is conventional, whereas the punctuation of an adverb clause that follows an independent clause is not.

Although a predicative adverb clause (i.e., after an independent clause) beginning with *whereas*, denoting a contrast, is often demarcated by a comma, demarcation seems arbitrary for demarcating the following meanings: reason (marked by *because*); condition (marked by *if* or *when*); objective (marked by *so that*). However, the justification could be for segregational emphasis.

Between some coordinated syntactic units

Example 4: Independent clauses of a compound sentence
(Methods section)
A lipid fraction was incubated with 6% ethanolic KOH and released fatty acids were extracted with hexane.

Revision
A lipid fraction was incubated with 6% KOH, and released fatty acids were extracted with hexane.

Notes

A frequent usage of the comma is between independent clauses of a compound sentence connected by a coordinating conjunction (*and*, *but*, *or*). In the example, a comma is necessary before *and* to indicate that *release fatty acids* is the subject of the second independent clause and not the object of *with*. Therefore, to maintain consistency the comma should always be used between independent *and*-connected clauses of a compound sentence, even when such subject identification is not necessary.

Example 5: Coordinated noun phrases in series
(Results section: results statement)
Treatment with indomethacin inhibited the formation of prostaglandin E, thromboxane A or 6-keto PGF.

Revision
Treatment with indomethacin inhibited the formation of prostaglandin E, thromboxane A, or 6-keto PGF.

Notes

To a non-expert, the last item *6-keto PGF* could be a synonym of the penultimate item *thromboxane A*. However, the presence of a comma minimises such misreading.

If an *and* replaces *or*, misreading the last two items as synonyms is unlikely. But another type of misreading is possible.

There is controversy whether a comma is necessary before *and* (the serial/Oxford comma). Often the comma is omitted before *and*, because the comma is considered to be an equivalent of *and*. However, in some listings, the comma before *and* is necessary (*my parents, Albert Einstein, and Madame Curie*). Because the comma after *my parents*, functions as a weak colon, without the second comma, Einstein and Curie are my parents. Although this sentence pattern is infrequent, if even one exists in a journal article the serial comma should be routinely used for constancy.

Tabular Summary

Comma omission	Revision	Punctuation addition
1. Conjunctive adverb independent clause	Conjunctive adverb, independent clause	Comma
2. Prepositional phrase independent clause	Prepositional phrase, independent clause	Comma
3. Adverbial clause independent clause	Adverbial clause, independent clause	Comma
4. Independent clause and independent clause	Independent clause, and independent clause	Comma
5. Noun phrase, noun phrase or noun phrase	Noun phrase, noun phrase, or noun phrase	Comma

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This is called the hash, pound, or number character. A hashtag is a keyword or set of keywords that is preceded by the # character. It is used in social media to create a thread of conversations around a specific theme or topic conveyed in short texts or microblogs. It is commonly used in Twitter, Instagram, YouTube, Pinterest, etc.

A dictionary of most common hashtags can be found at https://www.hashtags.org/definition/~h/.

For your info, EMWA is compiling a list of standarised hashtags for our social media use.

@ This is called the "at" sign or symbol. The @ sign is part of email addresses and social media user names ("handles"). Our EMWA handles are as follows: @Official_EMWA (Twitter), @EMWA (LinkedIn), and @europeanmedicalwritersassociation (Facebook)

The two most important keys on your keyboard

Pharmacovigilance

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Editorial

The PV section in this issue opens the door to a very interesting topic: ecopharmacovigilance. This article is the result of a collaboration among volunteers of EMWA's Pharmacovigilance Special Interest Group (PV SIG) and the Ecopharmacovigilance SIG at the International Society of Pharmacovigilance (ISoP). The authors have realised that there is an urgent need to measure the impact and understand the current picture of the problem of unintended environmental exposure to pharmaceuticals. Awareness must be raised between the different stakeholders through education and training.

While the problem of incorrect disposal of pharmaceutical waste is a well-known and relevant issue from a perspective of environmental risk and sustainability, I think that only very few among us have ever regarded it as a potential area for synergy and risk minimisation from a pharmacovigilance perspective. This article will open our mind to new perspectives!
I wish everyone happy reading!

Tiziana von Bruchhausen
Chair of the PV SIG

Ecopharmacovigilance: A review of cause, impact, and remedies

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Introduction

Pharmaceuticals contaminating the environment is a well-known, multidimensional problem. Biologically active pharmaceuticals and their metabolites can have off-target effects when they enter the environment. The UN Environment Program has identified environmentally persistent pharmaceutical products (EPPPs) as a serious problem requiring urgent policy remedies.[1] Recognising these grave concerns, some regions,[2] companies,[3,4] and countries such as Bhutan, Canada, Colombia, Ghana, India, Israel, Liberia, Lithuania, Sri Lanka, the European Union, and the United States, among others, have enacted measures to reduce the environmental impact of pharmaceuticals.[5–12] An example is the European Union where during drug development, manufacturers are mandated to conduct environmental impact testing of human (and veterinary) drugs (both for GMOs and non-GMOs), and include clear wording in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) on proper drug disposal.[13,14] However, other countries have inadequate or non-existent guidelines and regulations.

Sources of pharmaceutical waste

Pharmaceutical waste comprises a broad set of waste products from using or disposing of medicine and medicinal products. The WHO defines pharmaceutical waste as "expired, unused, spilled and contaminated pharmaceutical products, prescribed and proprietary drugs, vaccines and sera that are no longer required and due to their chemical or biological nature, need to be disposed of carefully".[15] According to the National Health Service, of the United Kingdom, pharmaceutical waste in the healthcare setting can arise from the following:[16,17]

1. **Non-compliance:** Patients do not take medicines as prescribed. For example, taking at irregular intervals or in incorrect doses leads to unused drugs which are eventually discarded.
2. **Intentional non-adherence:** Patients stop taking medication due to adverse events or personal beliefs.
3. **Unintentional non-adherence:** Patient forgets and stops taking medicines or fails to take them at correct time intervals due to forgetfulness.
4. **Non-preventable waste:** Patients die, and medications remain unused, or a change in treatment means current dispensed medicines are no longer required.
5. **Preventable waste:** Patient stockpiles medicines "just in case." All items from repeat prescriptions are dispensed even if the patient no longer takes medications.

Additionally, sources of pharmaceutical waste include improperly disposed medications, effluents from pharmaceutical manufacturing plants, excretion of metabolites by patients, and the irrational use of medications in agriculture, among others.[18] Manufacturers sometimes include information on safe disposal of expired medications in the SmPC and PIL, but consumers do not always follow such guidelines.

The burden of improper disposal of pharmaceutical waste

Over time, little attention has been paid to the environmental impact of pharmaceuticals. Until recently, very few studies have estimated the burden of pharmaceutical products on the environment; these studies are limited to a few countries. The methods used were often non-standardised, making comparisons difficult. Drug usage in both humans and animals is ever-increasing. One study projects that the global consumption of veterinary antimicrobials will be more than 100,000 tons by 2030.[19] Earlier reviews, mostly from high-income countries, demonstrated the presence of pharmaceuticals in water bodies.[18] However, one of the most extensive studies estimating the presence of medications in 1052 rivers across 104 countries showed that the most contaminated rivers were in the low-middle-income countries of sub-Saharan Africa, South Asia, and South America.[20] The need for the safe disposal of medicines is an issue today, but awareness among healthcare

professionals and consumers is low.

There are already some examples of regulations in this field such as those from the EMA, and the US FDA.[13,21] For example, in Europe, throughout drug development, manufacturers are mandated to conduct environmental impact testing of human (and veterinary) drugs (both for GMOs and non-GMOs) and include clear wording in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) on proper drug disposal[13] Provision of clear disposal guidelines by manufacturers in the SmPC and PIL[22] and strict adherence by end users can help to decrease the environmental load of medicines. Some authors argue that the burden of responsible disposal should be shared between government, patients, and pharmaceutical companies.[23] Pharmacovigilance professionals can be at the forefront and create a movement, especially since they are in a unique position to educate all relevant stakeholders about safe medicine use and its disposal. Proper patient counselling on safe medication disposal can significantly impact this critical public health challenge. A practical approach would be to prioritise this issue in the training curricula of all healthcare workers. Establishing cost-effective and acceptable government-run collection and disposal systems constitute a long-term solution. Manufacturers and regulatory authorities need to work together to develop a framework for environmental risk assessment of medications and establish and evaluate risk minimisation activities.[24] This multidisciplinary approach requires all the stakeholders – governments, non-governmental organisations, physicians, pharmacists, patients and the public, to work synergistically to reduce the burden of pharmaceuticals on the environment.

How can we integrate ecopharmacovigilance into existing pharmacovigilance systems?

Pharmacovigilance comprises a whole range of routine activities and an expanding scope of unique activities beyond the regular reporting of Adverse Drug Reactions. As described in the EMA Good Pharmacovigilance Practices guidelines, additional pharmacovigilance activities have been recommended to identify delayed safety concerns.[25] Some regulatory agencies such as the EMA[13] require the manufacturer to conduct a risk assessment that estimates the concentrations that will be found in the environment in order to gain market approval. Low concentrations (defined by USFDA as less than one part per billion) are assumed to pose only acceptable risks (but still a risk!).[26] We now know that pharmaceuticals' environmental impacts are often so slow and inconspicuous that they go unnoticed until it is very late. Ecopharmacovigilance could very well be proposed as an additional risk minimisation activity. Some authors have proposed targeted implementation focusing on the monitoring of the occurrence of high-priority pharmaceuticals in environmental samples, the management of primary emission sources, legislation and research on high-priority pharmaceutical pollutants, as well as the targeted educational strategies for specific vital populations.[27] These proposals, in turn, can influence the health of these animals and eventually humans.

The ongoing success of pharmacovigilance programmes in various countries is a good reason to suggest that pharmacovigilance is best positioned to take on extra activities, dealing specifically with the effects pertaining to the environment. Ecopharmacovigilance can be easily incorporated within the routine activities of existing pharmacovigilance programmes with close collaborations with manufacturers and responsible regulatory agencies.[28] Through urgent passing and implementation of strict regulations, there remains the hope of reversing or preventing further impact on the environment and food chain. Education and training in ecopharmacovigilance and environmentally conscious prescribing are essential components identified by some researchers that could significantly impact how medicines are used and disposed of.[29]

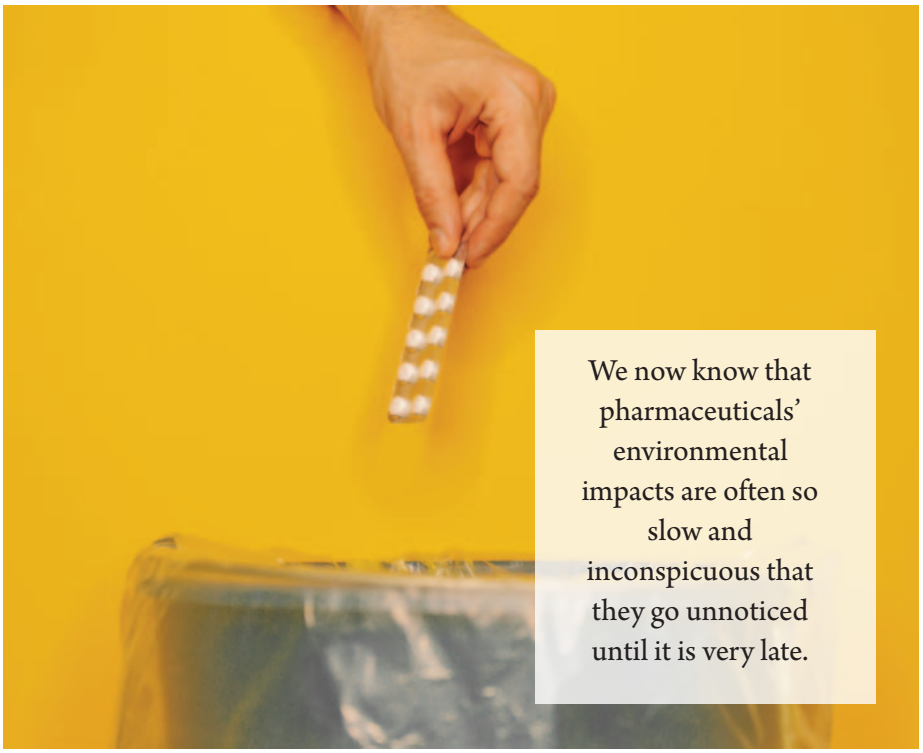
Taking cues from operational history of pharmacovigilance programmes, successful strategies such as spontaneous reporting, intensive monitoring and database studies, have been proposed as starting points for ecopharmacovigilance.[30] These activities can be implemented for continued environmental risk assessment of products approved by the pharmaceutical regulator.

Conclusion

The presence of pharmaceuticals and their active metabolites in the environment is a cause for great concern. A concerted multidisciplinary approach is needed to tackle this menace. Countries which have non-existent or inadequate environmental regulations can learn from success stories like the EMA and USFDA. The current scope of pharmacovigilance activities must be extended to include aspects of ecopharmacovigilance, and "pharmacovigilantes" can easily contribute their skills toward this cause. Lessons drawn from the successes and challenges of ecopharmacovigilance will be used to improve the discipline further.

Disclosures and conflicts of interest

The authors declare no conflicts of interest.



References

1. UNEP. Environmentally Persistent Pharmaceutical Pollutants (EPPPs) | UNEP – UN Environment Program [cited 2022 Sep 12]. Available from: https://www.unep.org/explore-topics/chemicals-waste/what-we-do/emerging-issues/environmentally-persistent-pharmaceutical.
2. European Commission. Pharmaceuticals and the Environment [cited 2022 Sep 12]. Available from: https://health.ec.europa.eu/medicinal-products/pharmaceuticals-and-environment_en.
3. Sanofi. Pharmaceuticals in the Environment Factsheet. 2022, p. 1–9 [cited 2022 Sep 12] Available from: https://www.sanofi.com/dam/jcr:e4bab2f5-26a3-4140-8744-920a8939cd13/Pharmaceuticals-in-the-environment.pdf.
4. AstraZeneca. Pharmaceuticals in the environment. [cited 2022 Sep 23]. Available from: https://www.astrazeneca.com/sustainability/environmental-protection/pharmaceuticals-in-the-environment.html.
5. Motiekaityte V, Venckus Z. Legal regulation of pharmaceutical waste management in Lithuania. Prof Stud Theory Pract. 2016;2(17):26–33.
6. Prakash V, Palaniraj N. Legal aspects and process of biomedical waste management practices in India. J Exclus Manag Sci. 2014;3(1).
7. Barnett-Itzhaki Z, Berman T, Grotto I, Schwartzberg E. Household medical waste disposal policy in Israel. Isr J Health Policy Res. 2016;5(1):1–8. doi:10.1186/s13584-016-0108-1
8. Drug Regulatory Authority. Guideline for disposal of pharmaceutical waste (1st Edition , 2014). 2014;1–12 [cited 2022 Oct 5]. Available from: http://dra.gov.bt/wp-content/uploads/2015/07/Guideline-for-disposal-of-Pharmaceutical-Waste.pdf
9. National Medicine Regulatory Authority. Guideline for safe disposal of expired and unwanted pharmaceuticals. 2019;1–14 [cited 2022 Oct 5] Available from: https://nmra.gov.lk/images/PDF/draft_guidelines/Guidelines-for-safe-disposal-of-expired—unwanted-pharmaceutical.pdf.
10. Food and Drugs Authority, Ghana. Guidelines for safe disposal of unwholesome products. 2019 [cited 2022 Oct 5]. Available from: https://nmra.gov.lk/images/PDF/draft_guidelines/Guidelines-for-safe-disposal-of-expired--unwanted-pharmaceutical.pdf
11. Liberia Medicines and Health Products Regulatory Authority. The Liberia medicines and health products guideline for pharmaceutical wastes [cited 2022 Oct 5]. Available from: https://lmhra.gov.lr/download/pharmaceutical-waste-management-guideline/#.
12. Küster A, Adler N. Pharmaceuticals in the environment: Scientific evidence of risks and its regulation. Philos Trans R Soc Lond B Biol Sci. 2014;369(1656):20130587. doi:10.1098/rstb.2013.0587
13. EMA. Guideline No. 4447/00 on the Environmental risk assessment of medicinal products for human use. 2006 [cited 2022 Sep 12]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf
14. EMA. Environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs) – Scientific guideline 2007 [cited 2022 Sep 12]. Available from: https://www.ema.europa.eu/en/environmental-risk-assessments-medicinal-products-containing-consisting-genetically-modified
15. WHO. Safe management of waste from healthcare activity. 2014;1–242.
16. Trueman P, Taylor D, Lowson K, et al. Evaluation of the scale, causes, and costs of waste medicines. Report of DH funded national project. York Heal Econ Consort Sch Pharmacy, Univ London, York London 2010 [cited 2022 Oct 23]; Available from: http://php.york.ac.uk/inst/yhec/web/news/documents/Evaluation_of_NHS_Medicines_Waste_Nov_2010.pdf.
17. Tudor TL, Noonan CL, Jenkin LET. Healthcare waste management: A case study from the National Health Service in Cornwall, United Kingdom. Waste Manag. 2005 1;25(6):606–15.
18. Kmmerer K. Pharmaceuticals in the environment [cited 2022 Oct 23] Available from: https://www.annualreviews.org/doi/abs/10.1146/annurev-environ-052809-161223
19. Tiseo K, Huber L, Gilbert M, et al. Global trends in antimicrobial use in food animals from 2017 to 2030. Antibiotics. 2020;9(12):1–14.
20. Wilkinson JL, Boxall ABA, Kolpin DW, et al. Pharmaceutical pollution of the world's rivers. Proc Natl Acad Sci USA. 2022;119(8):e2113947119. doi:10.1073/pnas.2113947119
21. FDA. Environmental Impact Considerations | FDA 2022 [cited 2022 Nov 9]. Available from:

https://www.fda.gov/animal-veterinary/ development-approval-process/ environmental-impact-considerations.
22. EMA. Questions and answers on "Guideline on the environmental risk assessment of medicinal products for human use". EMA/CHMP/SWP/ 44609/2010. 2015;44:19.
23. Karim-Nejad L, Pangilinan K. How should responsibility for proper medication disposal be shared? AMA J Ethics. 2022;24(10): E971–79. doi:10.1001/amajethics.2022.971
24. Jose J, Sandra Pinto J, Kotian B, et al. Comparison of the regulatory outline of ecopharmacovigilance of pharmaceuticals in Europe, USA, Japan, and Australia. Sci Total Environ 2020;709:134815. doi:10.1016/j.scitotenv.2019.134815
25. EMA. Guideline on good pharmacovigilance practices (GVP), Module V – Risk management systems (Rev 2) EMA/838713/2011. 2017 [cited 2022 Oct 5]. Available from: https://www.ema.europa.eu/en/documents/scientificguideline/guideline-good-pharmacovigilance-practices-module-vrisk-management-systems-rev-2_en.pdf
26. Rahman SZ, Khan RA, Gupta V, Uddin M. Pharmacoenvironmentology – A component of pharmacovigilance. Environ Health. 2007;6:20.
27. Wang J, Li S, Zhu Y, et al. Targeted eco-pharmacovigilance as an optimized management strategy for adverse effects of pharmaceuticals in the environment. Environ Toxicol Pharmacol 2021. 1;82. 103565. doi:10.1016/j.etap.2020.103565
28. Kümmerer K, Velo G. Ecopharmacology: A new topic of importance in pharmacovigilance. Drug Saf. 2006;29(5):371–3. doi:10.2165/00002018-200629050-00001
29. Wang J, Li S, He B. Chinese physicians' attitudes toward eco-directed sustainable prescribing from the perspective of ecopharmacovigilance: A cross-sectional study. BMJ Open 2020 1;10(6):e035502.
30. Wang J, Zhang M, Li S, He B. Adapting and applying common methods used in pharmacovigilance to the environment: A possible starting point for the implementation of eco-pharmacovigilance. Environ Toxicol Pharmacol. 2018;61:67–70. doi:10.1016/j.etap.2018.05.020

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Regulatory Matters

Editorial

In recent years, systems biology is not only being applied in fundamental science but also in drug development and healthcare. The application of real-world data in clinical research generates a large volume of data and information that is difficult to handle without a proper tool to process, decode, and interpret the data. That is where systems biology comes into play. In this article, Arunon Sivananthan introduces the idea of applying systems biology in clinical research and how it may play an important role in facilitating the process of drug development.

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Systems biology and real-world data as drivers of change in drug research and development

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Introduction

Research and development of drugs for polygenic diseases is complex, time-consuming, and has a high attrition rate.[1] Drug attrition is in part related to genetic heterogeneity, multifaceted pathophysiology, and complex environmental conditions that are difficult to reproduce within the context of randomised controlled trials (RCTs). Whilst RCTs have been instrumental in establishing the efficacy and safety of drugs since the 1960s.[2,3] RCTs are time-consuming, costly, and have limited applicability in clinical practice.

Studies into human physiology over the past several decades have developed qualitative understanding of the intracellular molecular interactions to whole-body phenotypic responses. Earlier reductionist approaches usually took the form of the "single path transduction model", which described the interactions of single drugs with a single receptor, thereby facilitating the discovery of ground-breaking drugs like propranolol or cimetidine.[4] Recently, advances in genetics, molecular, and systems biology techniques is fuelling the latest paradigm shift in drug development towards the use of "biological network transduction models" to analyse the effect that drugs have on biological networks through multiple interactions.

Systems biology uses a collection of quantitative experimental and computational methods to reveal the information flow between the genes, proteins, and metabolites essential in the functional pathways that exist among cells, tissues, organs, and organismal-level phenotypes. Systems biology helps to develop an understanding of the functional units contributing to disease phenotypes, ultimately leading to the identification of molecular mechanisms of drug action, and the design of therapeutic strategies that modify disease processes instead of simply controlling symptoms.[5]

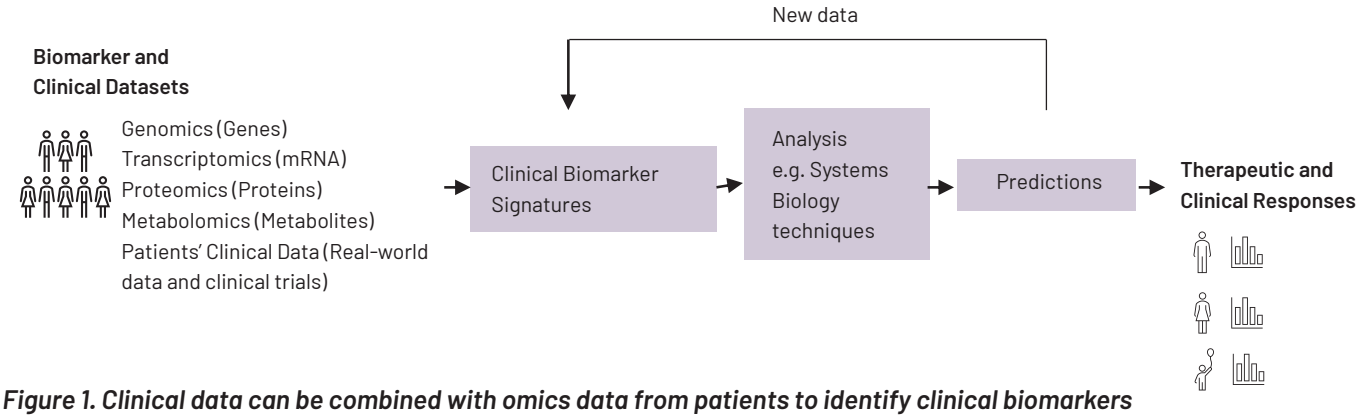
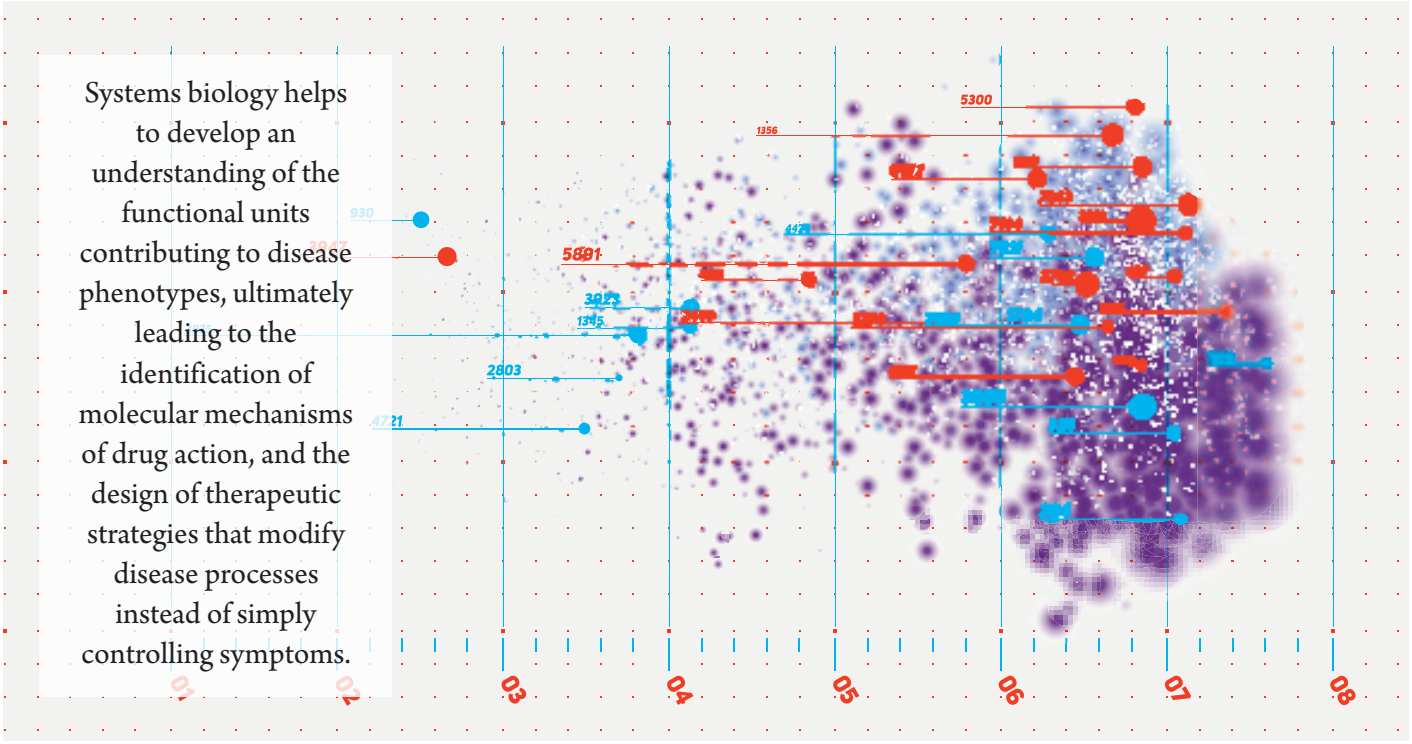


Figure 1. Clinical data can be combined with omics data from patients to identify clinical biomarkers
Using systems biology techniques in the analysis, these clinical biomarkers inform the construction of predictive models of disease course and patient response to therapy, thereby helping to form and update the biological model.



This article discusses the role of systems biology techniques in identifying and describing disease phenotypes, and the application of real-world data (RWD) and systems biology techniques to aid drug development.

The role of systems biology techniques in disease characterisation

The fundamental principle of systems biology is that any biological phenotype of interest to the study of human physiology is the outcome of a multitude of molecular interactions.[6] These molecular interactions can occur at any one time at and between the cellular-, tissue-, organ-, and organismal-levels.[6] Diseases are the result of disturbed molecular interactions, meaning it is essential to investigate numerous interacting partners and analyse the networks for accurate diagnoses and understanding of its mechanisms.[7,8]

Factors that can disrupt or perturb the network may be intrinsic, such as mutations in certain genes, or extrinsic, like environmental cues, to the human system.[9,10] The native network will respond differently to each disruption depending on unique robust characteristics, thereby producing distinct phenotypic responses that constitute a corresponding pathological state.[11] Studies into individual disruptions and development of "biological network transduction models" require investigations at the genomic, transcriptomic, miRNomic, proteomic, and metabolomic levels. Large-scale data collection is made possible with advanced wet-lab technologies such as quantitative polymerase chain reaction (qPCR), mass spectrometry, and next generation sequencing. Fitting the results together to analyse large-scale databases is aided by systems biology techniques.

Real-world data and therapeutic evaluations

Regulatory approval of drugs and medicinal products has shifted its focus to the evaluation of therapeutic interventions based on tailor-made precision treatments in stratified patient populations,[4] which is often supported using RWD. RWD provides long-term data generated from clinical practice that can aid the research and development of therapeutic interventions. A major value of RWD is that they fill knowledge gaps between controlled clinical trials with the information regarding patients' health in clinical practice.

RWD are data and stored information related to the patient's health status derived from a variety of sources such as patient registries, health institutions, social media, and patient-generated data from wearables.[12,13] The analysis of RWD includes the use of systems biology techniques and generates real-world evidence (RWE) for demonstrating drug effectiveness and safety for marketing authorisation and for advancing drug development.[14] Combining RWD with prediction models developed by systems biology can contribute significantly to support regulatory decision-making (Figure 1).[15]

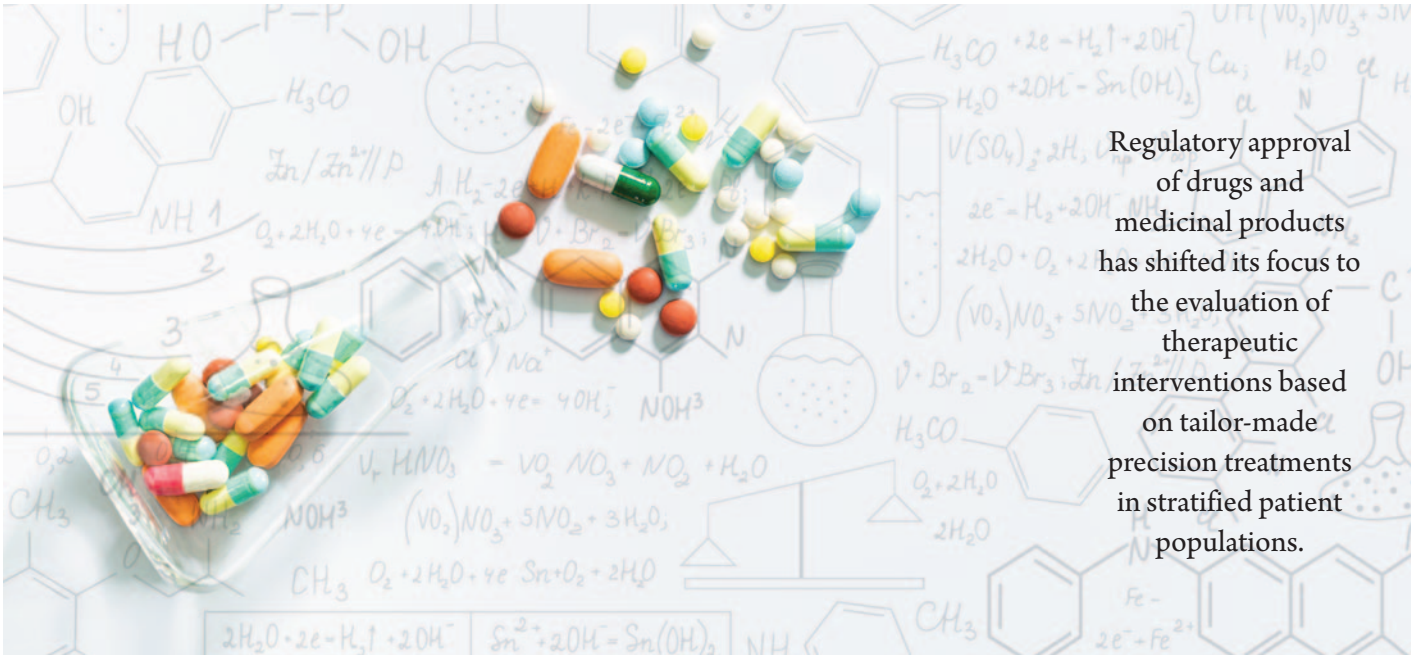
Hybrid study designs incorporating RWD or RWE have been applied in clinical trials for regulatory decision-making. The hybrid study designs were used:[16]

1. for exploratory new drug submissions that use RWE to gain insights to clinical outcome or safety data;
2. as methods for single-arm trials that require external controls; and
3. in clinical trials that need RWE to satisfy post-marketing requirements for additional safety or effectiveness to support a regulatory decision.

Hybrid study designs that are better equipped to capture long-term outcomes should harness methodologies such as decentralisation (e.g. trained nurses), direct-to-patient approaches (e.g. wearables), and databases (e.g. registries, claims).[16]

Systems biology in action

Systems biology approaches have been used to investigate fundamental processes such as metabolic rewiring that determine T cell activation.[17] The value of combining metabolomic and computational approaches have enabled researchers to overcome complex cell regulatory networks that have hindered the discovery of the metabolic requirements of certain biological systems. For example, Puleston,



Regulatory approval of drugs and medicinal products has shifted its focus to the evaluation of therapeutic interventions based on tailor-made precision treatments in stratified patient populations.

et al. (2021)[18] and Wagner, et al. (2021)[19] applied metabolic, computational, and genetic approaches to demonstrate the important role of polyamine metabolism in determining the path of T helper cell fate commitment.

Recently Wimmers et al. (2021)[20] employed a multi-omic approach that used systems biology approaches to assess long-term immune responses to influenza vaccines. These researchers compared the human immune landscape in response to three types of vaccinations, i.e. the trivalent inactivated seasonal influenza vaccine and the avian H5N1 pre-pandemic influenza vaccine with and without an adjuvant. Their analysis involved a comparison of epigenomic imprinting, transcriptional profiles, and chromatin accessibility at single-cell level, as well as cytokine production that respond to viruses at different time points after vaccination. The two key outcomes were: i. epigenetic effects of vaccination lasted 6 months and were more pronounced in innate immune cells; ii. chromatin accessibility to loci mediated by AP-1 transcription factors were reduced over time and correlated with lower production of inflammatory cytokines.

Another example of how systems biology was used in clinical research is illustrated with the pivotal role that the monoclonal antibody daclizumab plays in multiple sclerosis (MS). Daclizumab prevents the formation of the high affinity IL-2 receptor[21,22] and obstructs FoxP3$^+$ T-regulatory cells activity.[23,24] Should this observation be interpreted in a linear, reductionist fashion, a conclusion may be that T-regulatory cells do not play an immunoregulatory role in MS, with negative consequences. In fact, daclizumab also activates the regulatory cell population, CD56^{bright} NK cells,[25] which are part of the same *in vivo* functional network as T-regulatory cells.[24] The steady state of T-regulatory cell activation and proliferation achieved by daclizumab treatment is clearly beneficial for MS patients.

Summary

Systems biology has a positive impact on clinical research by combining and examining data from various omics approaches. The ability to combine large volumes of data using experimental and computational sources enable the development of complex models of molecular interactions. These models can provide valuable insight to aid drug development such as drug/target interactions, drug repositioning, and the identification of novel disease networks.

With the aid of systems biology, the incorporation of RWE plays an important part in developing models that are robust enough to develop our understanding of disease states. Observing the consequences of changes to these models, like genetic mutations or differences in medicinal regimens or target group, may facilitate the process of drug development.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by his employer or EMWA.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. Waring MJ, Arrowsmith J, Leach AR, et al. An analysis of attrition of drug candidates from four major pharmaceutical companies. Nat Rev Drug Discov. 2015;14:475–86. doi:10.1038/nrd4609
2. US FDA, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products [cited 2022 Dec 22]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products
3. US FDA. Kefauver-Harris Amendments Revolutionized Drug Development [cited 2022 Dec 22]. Available from https://www.gvsu.edu/cms4/asset/F51281F0-00AF-E25A-5BF632E8D4A243C7/kefauver-harris_amendments.fda.thalidomide.pdf
4. Danhof M, de Jongh J, de Lange ECM, et al. Mechanism-based pharmacokinetic-pharmacodynamic modelling: Biophase distribution, receptor theory, dynamical systems analysis. Annu Rev Pharmacol Toxicol. 2007;47:357–400.
5. Danhof M. Systems pharmacology – towards the modelling of network interactions. Eur J Pharm Sci. 2016;94:4–14. doi:10.1016/j.ejps.2016.04.027
6. Friboulet A, Thomas D. Systems biology –

an interdisciplinary approach. Biosens Bioelectron. 2005;20(12):2404–7. doi:10.1016/j.bios.2004.11.014
7. Houtman JCD, Barda-Saad M, Samelson LE. Examining multiprotein signalling complexes from all angles. FEBS J. 2005;272(21):5426–35. doi:https:10.1111/j.1742-4658.2005.04972.x
8. Terentiev A, Moldogazieva N, Shaitan K. Dynamic proteomics in modelling of the living cell. Protein-protein interactions. Biochem (Moscow). 2009;74(13): 1586–607. doi:10.1134/S0006297909130112
9. Stelling J, Sauer U, Szallasi Z, et al. Robustness of cellular functions. Cell. 2004;118(6):675–85. doi:10.1016/j.cell.2004.09.008
10. del Sol A, Balling R, Hood L, Galas D. Diseases as network perturbations. Curr Opin Biotechnol. 2010;21:566–71. doi:10.1016/j.copbio.2010.07.010
11. Kitano H, Oda K, Kimura T, et al. Metabolic syndrome and robustness tradeoffs. Diabetes. 2004;53:S6–S15. doi:10.2337/diabetes.53.suppl_3.S6
12. EMA. Update on Real World Evidence Data Collection [cited 2022 Dec 22]. Available from: https://www.ema.europa.eu/en/documents/presentation/update-real-world-evidence-darwin-eu-gianmario-candore_en.pdf
13 US FDA. Framework for FDA's Real World Evidence Program [cited 2022 Dec 22]. Available from https://www.fda.gov/media/120060/download
14. United States Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products [cited 2022 Dec 22]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drug-and-biological-products
15. Skovlund E, Leufkens HGM , Smith JF. The use of real-world data in cancer drug development. Euro J Cancer. 2018;101: 69–76. doi:10.1016/j.ejca.2018.06.036
16. Andre ED, Reynolds R, Caubel P, et al. Trial designs using real-world data: The changing landscape of the regulatory approval process. Pharmcoepidemiol Drug Saf. 2020;29:1201–12. doi:10.1002/pds.4932
17. Chapman NM, Boothby MR, Chi H. Metabolic coordination of T cell quiescence and activation. Nat Rev Immunol. 2020;20:55–70. doi:10.1038/s41577-019-0203-y
18. Puleston DJ, Baixauli F, Sanin DE, et al. Polyamine metabolism is a central determinant of helper T cell lineage fidelity. Cell. 2021;184:4186–202. doi:10.1016/j.cell.2021.06.007
19. Wagner A, Wang C, Fessler J, et al. Metabolic remodeling of single Th17 cells reveals regulators of autoimmunity. Cell. 2021;184:4168–85. doi:10.1016/j.cell.2021.05.045
20. Wimmers F, Donato M, Kuo A, et al. The single-cell epigenomic and transcriptional landscape of immunity to influenza vaccination. Cell. 2021;184;3915–35. doi:10.1016/ j.cell.2021.05.039
21. Bielekova B, Richert N, Howard T, et al. Humanized anti-CD-25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon-beta. Proc Natl Acad Sci USA. 2004;101:8705–8. doi:10.1073/pnas.0402653101
22. Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): A phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010;9:381–90. doi:10.1016/S1474-4422(10)70033-8
23. Oh U, Blevins G, Griffith C, et al. Regulatory T cells are reduced during anti-CD25 antibody treatment of multiple sclerosis. Arch Neurol. 2009;66:471–9. doi:10.1001/archneurol.2009.16
24. Martin JF, Perry JS, Jakhete NR, et al. An IL-2 paradox: Blocking CD25 on T cells induces IL-2 driven activation of CD56 (bright) NK cells. J Immunol. 2010;185:1311-1320. doi:10.4049/jimmunol.0902238
25. Bielekova B, Catalfamo M, Reichert-Scrivner S, et al. Regulatory CD56^{bright} natural killer cells mediate immunomodulatory effects of IL-2R-alpha-targeted therapy (daclizumab) in multiple sclerosis. Proc Natl Acad Sci USA. 2006;103:5941–6.

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The Crofter: Sustainable Communications

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Editorial

Greetings from the croft. As medical writers/communicators who provide services to pharmaceutical companies, we are part of a pharmaceutical company's supply chain.

In this issue, we follow-up on EMWA's November 2022 Expert Series Seminar (ESS) on Sustainability by reprinting an interview with Dr Amy Booth and her research on carbon emissions and sustainable supply chains in the pharmaceutical industry. Dr Booth was the opening speaker of the ESS and her interview with Kim Thomas for *World Pharmaceutical Frontiers* captures her main findings and insights.

About a week after the ESS, I was excited to learn from Chris Winchester, CEO of Oxford PharmaGenesis, that the US Department of Health and Human Services (HHS) announced their sustainability plans for the healthcare sector at COP27,[1] which includes a joint plan with the National Health Service (NHS) of England to align procurement requirements for emissions and energy use. (These requirements will also cover pharmaceuticals.) That's collaboration, just as Dr Booth advocates! ☺

Best,
Kimi

Reference

1. HHS shares health sector emissions reduction and climate resilience announcements at COP27. 2022 [cited 2023 23 January]. Available from: https://www.hhs.gov/about/ news/2022/11/10/hhs-shares-health-sector-emissions-reduction-climate-resilience-announcements-at-cop27.html

Sustainable supply

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Corporate efforts to reduce environmental impact through policies targeted at limiting CO_2 output and dependence on fossil fuels come under the umbrella of ESG (Environmental, Social and Governance) – and sustainability throughout the supply chain is a significant part of that. Here, **Kim Thomas** speaks to **Dr Amy Booth** of the University of Oxford to find out how significant supply chains are in the journey to become carbon neutral.

Healthcare systems in the world's largest economies are responsible, on average, for nearly 5% of a nation's greenhouse gas emissions. If the global health care sector were a country, it would be the fifth largest polluter on earth.

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Tackling carbon emissions is now a priority for many healthcare systems. NHS England has set a net zero target of 2040 for the emissions it controls directly, and 2045 for the emissions of supply chain companies it can influence. Net zero involves cutting greenhouse gas emissions to as close to zero as possible. It differs from another frequently used term, carbon neutrality, which refers to balancing an organisation's greenhouse gas emissions against measures to offset those emissions, for example by planting trees.

A large chunk of the NHS's emissions (25%) comes from medicines, with anaesthetic gases and metered dose inhalers making up one-fifth of that chunk. The remaining 20% of emissions from medicines, according to an NHS document, are "primarily found in the manufacturing and freight inherent in the supply chain." The NHS's ambitious net zero commitment of necessity requires pharmaceutical suppliers to reduce their carbon emissions, who in turn require their suppliers to reduce their carbon emissions.

> Sanofi opened a continuous manufacturing plant in Massachusetts that emits 80% less carbon dioxide than its first-generation facility.

The Greenhouse Gas Protocol (GHGP) defines three scopes of emission, which can be used to measure an organisation's carbon output. Scope 1 refers to direct emissions from owned or directly controlled sources on site; scope 2 refers to indirect emissions from the generation of purchased energy, mostly electricity; scope 3 refers to all other indirect emissions that occur in producing and transporting goods and services, including the full supply chain.

Comparing emissions between companies is difficult

Amy Booth, MD, now undertaking a PhD at the University of Oxford on the environmental impact of health systems, has looked at the company reports of the 20 biggest (by prescription revenue) pharmaceutical companies to find out the extent to which the industry has engaged in emissions reduction. In a recently published conference paper, Booth and her co-authors found that 19 of the 20 companies had made commitments to reduce carbon emissions, with half committing to carbon neutrality and 40% to net zero emissions by a range of target years. Ninety percent had committed to improving reporting and reducing emissions across their supply chain.

While this is promising, Booth notes that it is difficult to compare what companies are doing: "Pharmaceutical companies have different baseline emissions, different baseline reporting years,

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run different operations, have different product scopes, and different employee sizes. This all affects their emissions, and makes comparing their commitments to reduce these emissions difficult. In addition, there are different ways companies can make commitments to reduce their emissions. Some make pledges to carbon neutrality, some to net zero, or some to reducing their emissions by a certain percentage by a certain year."

Some of the commitments are vague, she adds, lacking clarity about whether they refer to emissions only in scope 1 and 2, or across scopes 1, 2 and 3. Where companies have reported emissions, says Booth, most of the 20 companies had succeeded in reducing scope 1 emissions, and all had reduced scope 2 from their respective baseline years of reporting.

Positive initiatives cited by Booth include the implementation of renewable energy sources such as solar panels or wind farms. Many companies said that they were planning to "switch to more energy-efficient equipment, optimise manufacturing processes through green chemistry principles, and switching their vehicles from petrol or diesel to hybrid or electric".

GSK, for example, is undertaking a series of initiatives to meet its target of achieving net zero by 2030. At its large manufacturing facility in Irvine, Scotland, it intends to install two new wind turbines (8 MW) and a 56-acre, 20 MW solar farm. It is also redesigning its rescue metered dose asthma inhalers to use a lower greenhouse gas propellant that has the potential, the company says, to reduce greenhouse gas emissions from its inhalers by 90%.

Other companies are beginning to move from batch manufacturing – where materials are made in large bundles and are sometimes shipped to different locations between steps – to continuous manufacturing, a more efficient process in which drugs are made in a single location in an uninterrupted flow. Those who have adopted continuous manufacturing for part of their drug production include Eli Lilly, Vertex Pharmaceuticals, and Pfizer. Three years ago, Sanofi opened a continuous manufacturing plant in Massachusetts that emits 80% less carbon dioxide than its first-generation facility. It also reduces water and chemical usage by 91% and 94%, respectively.

> Once you start manufacturing a drug in a particular manner, if you want to make significant changes to that manufacturing process, you have to submit the proposed changes to regulatory bodies.

Supply chain diversity poses a challenge

While companies are taking positive steps to reduce scope 1 and 2 emissions, tackling scope 3 emissions is a tougher challenge. "The supply chain for any company is quite diverse," says Booth, "because you're not just looking at raw material suppliers or waste management companies, you're also looking at IT and lawyers and marketing and communications companies." Finding a standardised method for measuring and reporting emissions from such a diverse supply base is far from straightforward.

Some pharma companies have begun engaging with their supply chain, says Booth, through measures such as "implementing sustainability criteria into their vendor selection processes" and "committing to a programme where they assist suppliers to purchase more renewable energy". Measures they could require from suppliers include "sourcing raw materials, water, and energy sustainably or using recycled materials in packaging".

Pharma companies need to think both about how to bring suppliers on board and how to measure what suppliers are doing. One way of doing this, Booth suggests, could be through encouraging suppliers to report emissions and targets via the Ecovadis website, which provides a common platform, scorecard,

benchmarks, and performance improvement tools. The Carbon Disclosure Project is a similar initiative. By requiring suppliers to report to platforms such as these, they can determine the extent to which they are engaging with sustainability principles.

Yet achieving sustainability throughout the supply chain is far from straightforward. Heavy regulation restricts some of the measures companies can take. "If you look at green chemistry principles, a lot of that is about optimising the manufacturing process," says Booth. "But once you start manufacturing a drug in a particular manner, if you want to make significant changes to that manufacturing process, you have to submit the proposed changes to regulatory bodies and that can place limits on optimisation."

Collaboration is essential

Drug packaging is another example: "If you want to change the way you package a drug to make it more sustainable, you have to consider the regulations around packaging. Obviously, there are good reasons for these regulations in many cases, because you don't want your drug to change its composition or to be consumed by children, but those policies and regulations can be an obstacle to sustainability and I think that's why there needs to be collaboration with policy makers and regulators."

Some suppliers are small or medium-sized enterprises, Booth points out, that "might not necessarily have the capital to engage with a lot of these sustainability issues." For that reason, she says, collaboration is essential: Both pharma companies and government should be prepared to help suppliers as far as they can to meet sustainability targets so that no one gets left behind.

The biggest challenge, perhaps, is the need for standardising reporting of emissions, especially scope 3 emissions. While most of the pharma companies whose policies Booth reviewed use the GHGP reporting method, they use it inconsistently: "Not everyone reports on scope 3 emissions, and not everyone reports on all the categories of scope 3, so I think improving reporting and transparency is definitely needed. Getting data from suppliers is also going to be a challenge."

Agreement on how to implement sustainability throughout the supply chain and how to standardise measurement and reporting can only be achieved through cooperation. There are already encouraging examples of pharma companies working together. The International Pharmaceutical Aerosol Consortium (IPAC), for example, is coordinating a programme amongst large pharma companies to encourage patients to return inhaler devices to pharmacies for green disposal. The Pharmaceutical Supply Chain Initiative (PSCI), which promotes responsible practice in the supply chain, is committed to improving environmental sustainability and, at the end of 2021, created a Topic Team to focus specifically on the "measurement, management, and reduction of Scope 3 greenhouse gas emissions within the pharmaceutical sector".

Pharma is a large, complex sector, in which any single company has relationships with other pharma companies, with suppliers, with regulators, and with policy makers. This web of interrelationships means that progress on sustainability depends on cooperation, says Booth.

"There are a lot of gaps in innovative solutions to this problem, so finding those solutions, collaborating with academics, with people who are researching these novel solutions, is going to be important," she explains. "And then sharing those ideas as well – there is always competition between companies, but in this case, I think we need to put aside this competition, because our planet is at stake."

Kim Thomas, PhD, has been a freelance journalist for 25 years, writing for publications such as *The Guardian, Financial Times* and the *BMJ*. Her specialist area is health and medicine, and she has also published two books on postnatal PTSD and one about women committed to Broadmoor. Contact her at kimthomas@ntlworld.com

Amy Booth is a medical doctor and PhD candidate at the University of Oxford. Her research, which she has presented at national and international platforms, explores the climate change impact of the pharmaceutical supply chain and how to reduce it. Email: amy.booth@phc.ox.ac.uk.

CONTACT US

If you have ideas for themes or would like to discuss any other issues, please write to mew@emwa.org.

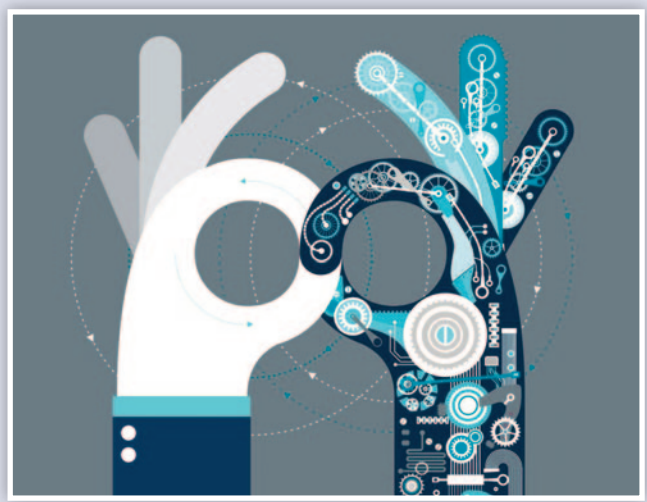
Upcoming issues of **Medical Writing**

June 2023:

Freelancing

Freelancing is becoming an increasingly popular option for medical writers and communicators, but it's not as straightforward as finding a few clients and getting paid. There's so much more involved. Freelancers are mini-business owners and to be successful, you need a plethora of skills, be self-motivated, driven, and adaptable and take the highs with the lows. In this issue, the authors will discuss what options are out there for freelancers, how to get started, and all the challenges that you may come across. Freelancing can be a lucrative business but addressing all the factors is key to being successful.

Guest Editors: Laura Kehoe and Satyen Shenoy
The deadline for this feature has now passed.



September 2023:

Automation/software

Streamlined complex medical report writing supported by artificial intelligence/machine learning is making its way into clinical regulatory writing. The medical writing automation's goal is to speed up and ease clinical development processes by reducing the time and cost involved in creating and keeping regulatory documents up to date. This issue will examine current issues, challenges, and opportunities towards human guided medical writing automation systems.

Guest Editors: Shiri Diskin and Daniela Kamir
The deadline for feature articles is June 1, 2023.

December 2023:

Biotechnology

Biotechnology uses biological systems and living organisms in R&D and production processes. Biotechnologies include biologic and biosimilar pharmaceuticals like monoclonal antibodies, vaccines and advanced therapy medicinal products, for example, gene and cell therapies and tissue engineered products. In addition, biotechnologies support the product lifecycle, for instance, in non-clinical work using in silico, in vitro, and animal testing methods. Also, support services personnel like those in biobanks and supply chains require an understanding of biotechnology. This issue focuses on the crucial role of writing and communications in biotechnology and product development.

Guest Editors: Jennifer Bell
The deadline for feature articles is September 1, 2023.

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