

# Medical Writing



## ALSO IN THIS ISSUE...

- Challenges and strategies for effective health communication in middle- and low income countries
- Three-part series on the value of medical writing
- Embracing a new era: The growing role of PR and social media in vet practice

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EUROPEAN MEDICAL WRITERS ASSOCIATION

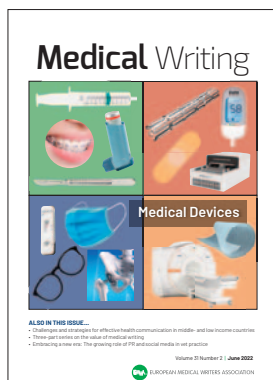


### **Medical Writing**

is the official journal of the European Medical Writers Association (EMWA). It is a quarterly journal that publishes articles on topics relevant to professional medical writers.

Members of EMWA receive Medical Writing as part of their membership. For more information, contact [mew@emwa.org](mailto:mew@emwa.org).

# Medical Writing



THIS ISSUE June 2022 | Volume 31 Number 2

## Medical Devices

“The contributions made by the MedTech industry during the COVID pandemic must be emphasised. A plethora of devices were mass-produced and delivered globally in a short span of time to those in dire need. This journal issue is dedicated to all those who made this possible and helped save thousands of lives during these unprecedented times.” Kelly Goodwin Burri and Namrata Upadhyay, Guest Editors

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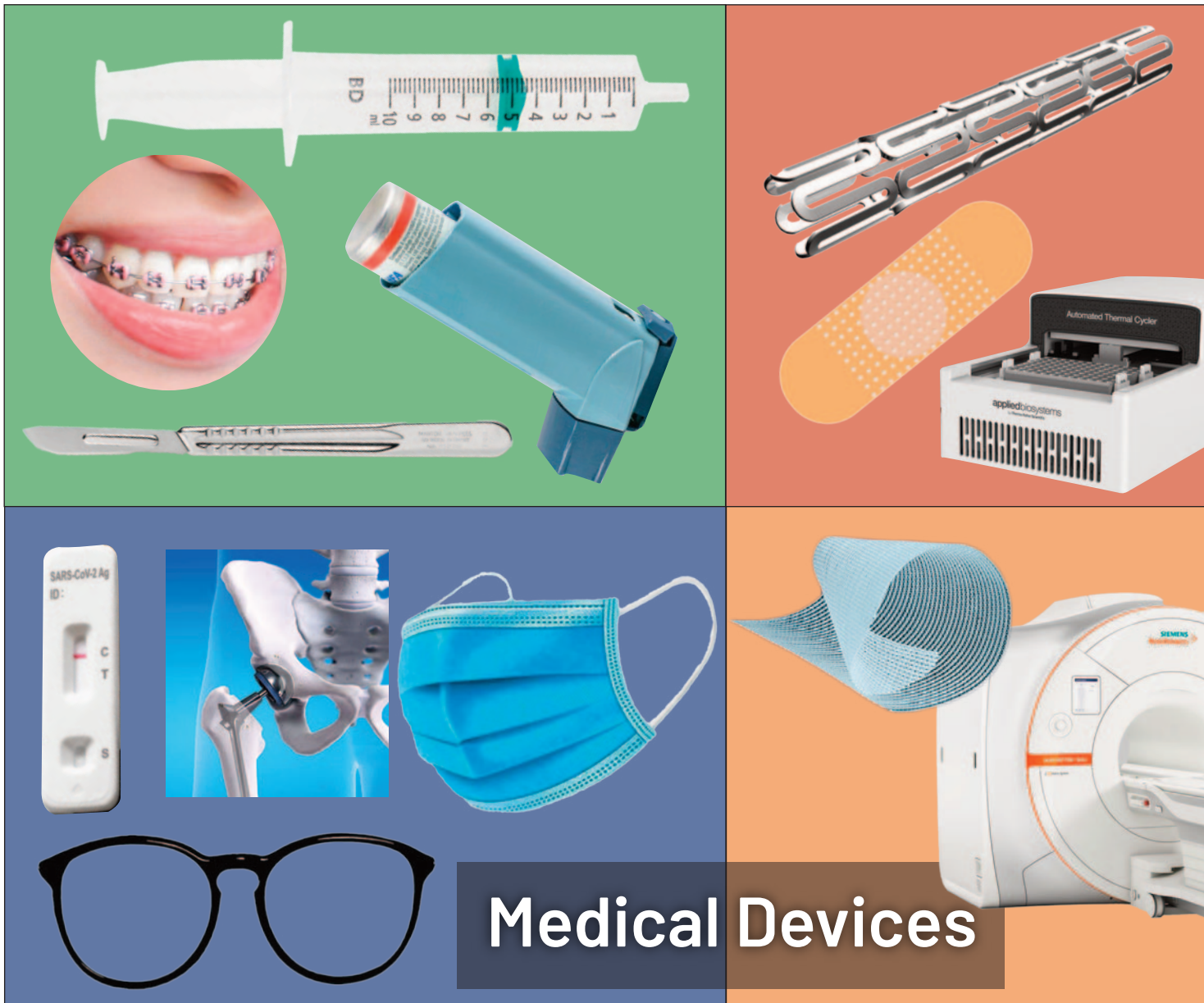
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# Medical Devices

**M**edical devices are at the core of healthcare forming a large share of the global healthcare market. With consistent advances in technology, MedTech is enhancing our lives more so now than a few decades ago owing to accelerated digitisation and software development.

The contributions made by the MedTech industry during the COVID pandemic must also be emphasised where a plethora of devices were mass-produced and delivered globally in a short span of time to those in dire need. This journal issue is dedicated to all those who made this possible and helped save thousands of lives during these unprecedented times.

Also coinciding with the COVID

## GUEST EDITORS



**Kelly Goodwin Burri**  
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pandemic has been the implementation of the EU medical device regulations (EU MDR 745/2017), which has been an uphill battle for most involved in this industry. With the uncertainties involved, either due to the remote working models owing to COVID 19, or the lack of prompt clarifications – be it with the number of notified bodies available to

handle the workload or the insufficient guidelines to support with the interpretation of the regulation – the medical device industry has nonetheless presented itself victorious on the other end.

This issue presents a glimpse into this tumultuous yet unbreakable world of MedTech presenting to you several articles on its inner workings.

**Roderick Mallia and Beate Walter** open the issue with an introduction to the differences between medical writing in the pharmaceutical industry and the medical device industry. This is a follow up to the first article written in 2017 by Beatrix Doerr et al on the differences between writing for pharmaceuticals and for medical devices.



This issue presents a glimpse into this tumultuous yet unbreakable world of MedTech presenting to you several articles on its inner workings.

They seamlessly define the parallels between both these worlds and present the variety of documentation involved, from a medical writing perspective, in both domains.

With pre-clinical testing being one of the first steps towards medical device production, it is apt to introduce the article by **Monica L. Meyer** on preclinical testing of implantable medical devices (IMDs) during new product development. The article walks us through the various stages in a device's product life cycle and facilitates our understanding of the multiple pre-clinical stages involved in device development with correlations also made from a regulatory perspective between US FDA and European submissions.

An important distinction made in the world of MDR is whether a device contains animal derived tissue or not. The article by **Russell T. Kronengold** caters to the intricacies of regenerative medical products derived from animal tissues and the regulatory requirements to be fulfilled with emphasis on the ISO 22442 standard.

With the pre-clinical testing stage complete, the device officially enters the clinical planning stage where one essential development under the MDR is that of defining the Clinical Development Plan. **Namrata Upadhyay** shares with us the essential content of a clinical development plan for medical devices and how a manufacturer can leverage it as a useful tool to enhance the quality of their overall clinical evaluation and technical documentation.

A well executed clinical development plan culminates into a medical device clinical investigation based on the risk classification of the device. **Jessica Norberg** introduces the clinical investigation plan and the reporting of the post-investigation results in the clinical investigation report. She helps readers to understand the differences between clinical studies conducted in pharma with those run for medical devices, emphasising the crucial role of a medical writer at this stage of device development.

With the pre-market clinical investigations completed, the next stage is in the creation of the clinical evaluation report (CER). **Gillian Pritchard** introduces the current trends in the writing of the clinical evaluation report 6 years after the introduction of MEDDEV 2.7/1 revision 4. The reader may walk through the various stages of CER writing with due diligence to the current challenges faced with the introduction of the MDR to the writing of this complex document.

Following market approval, the manufacturer is obliged to demonstrate a robust post market clinical follow up (PMCF). **Laura Collada Ali et al** provide valuable insights to the PMCF stage of device development – a welcome discussion owing to the stringency now placed by the MDR on the PMCF stage.



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#### Submissions:

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

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# The first year of application of the Medical Devices Regulation:

## Foreword from the European Commission

Ana Eva Ampelas, Mario Gabrielli Cossellu

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**A** lready 1 year has passed since the date of application of the new Medical Devices Regulation (EU) 2017/745 (MDR), replacing the previous Directives 90/385/EEC and 93/42/EEC from 26 May 2021, while for the new *In Vitro* Diagnostic Medical Devices Regulation (EU) 2017/746 (IVDR) the date of applicability is 26 May 2022, replacing the previous Directive 98/79/EC.

The medical devices sector is essential to the provision of healthcare to citizens and is an important player in both the European and global economy. As such, medical devices and *in vitro* diagnostic medical devices play a fundamental role in saving lives by providing innovative healthcare solutions for the diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease. Keeping this in mind, on 5 April 2017, two new Regulations were adopted, establishing a modernised and more robust EU legislative framework for medical devices to ensure better protection of public health and patient safety and improve the functioning of the internal market in medical devices.

Both Regulations require particularly far-reaching changes in the way the sector operates and important efforts for adaptation. This was made even more difficult with the COVID-19 pandemic in 2020-2021, seriously affecting the ability of the different actors involved to prepare for these changes.

The European Commission has been very active during these years and working closely with national competent authorities, notified bodies, and European associations representing health professionals, patients, and industry to ensure the smooth and effective implementation of the Regulations. This has included the adoption of a number of key implementing acts for designation of notified bodies, the availability of harmonised standards and common specifications, the ongoing development of the new European database on medical devices (“Eudamed”), the assignment of Unique Device Identifiers (UDI), the European Medical Device

Both Regulations require particularly far-reaching changes in the way the sector operates and important efforts for adaptation.

Adding to the post market stage is an article by **Karelia Tecante** and **Andre Sokija** that introduces the periodic safety update report (PSUR) and post market surveillance report (PMSR) documentation requirements under the MDR. The lack of a final guidance for creating these documents has been a challenge for everyone tasked with creating PSURs, even 1 year after MDR implementation.

With all the stages of device development covered, we then look towards the future of the MedTech domain which brings us back to the digitisation within the field over the past decade. When speaking of digitisation, one cannot ignore the introduction of artificial intelligence (AI). The last article by **Kirsten Dahm** introduces to us the new rules governing AI for devices in Europe owing to the limited guidance documents available to this rapidly growing and popular field.

We would like to thank all the authors for their contribution towards this issue of *Medical Writing* and welcome our readers to enhance their understanding of the inner workings of the medical device world. We hope that our readers enjoy this medical device focused journal issue as much as the authors and editorial team have enjoyed putting it together for them.

Happy reading!

**Namrata & Kelly**

### About the Guest Editors

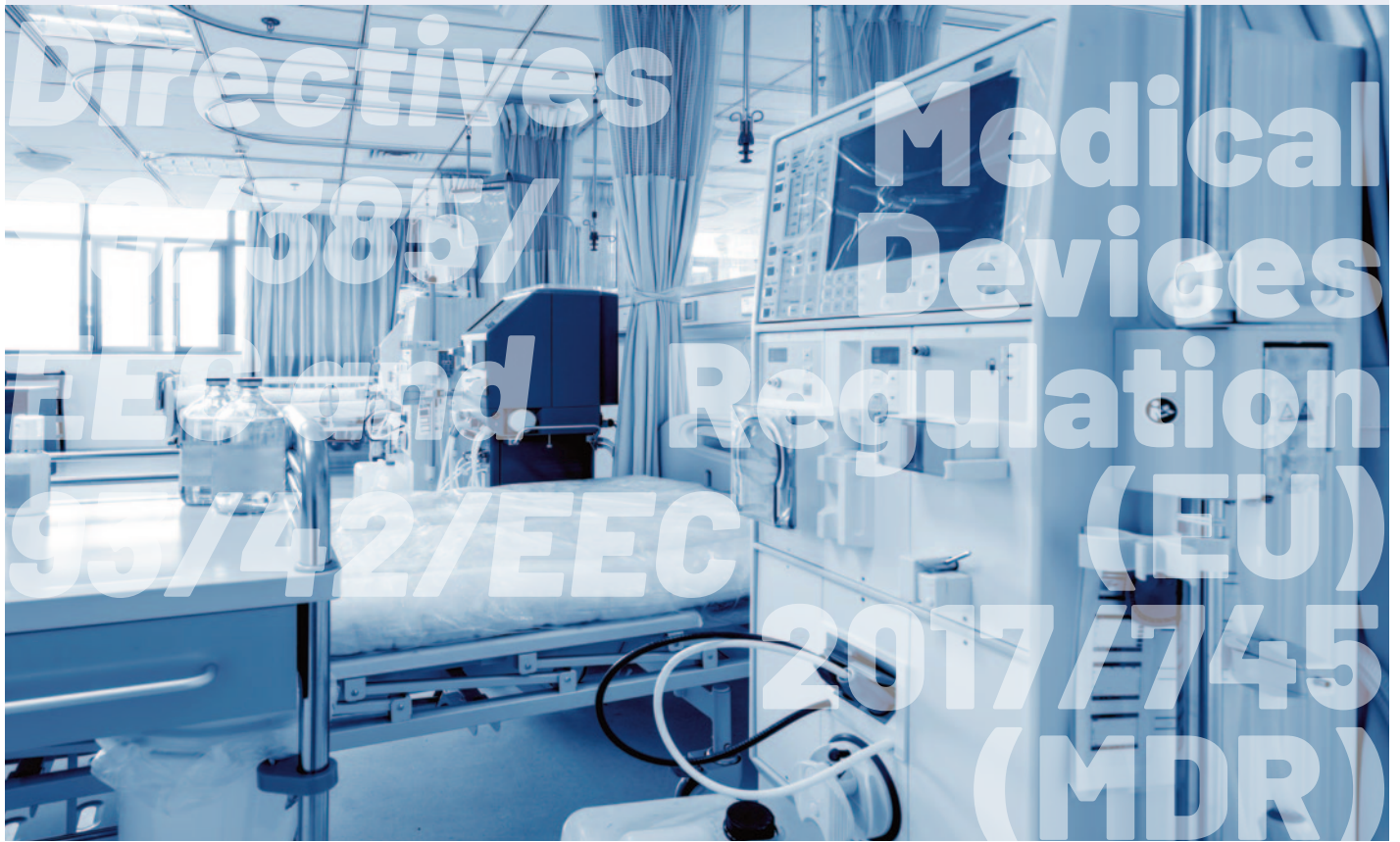


**Kelly Goodwin Burri** has a background in biomedical engineering and epidemiology with 20 years of professional experience in medical writing, clinical

research, and project management in both the pharmaceutical and medical device industries. She currently serves as the co-chair of EMWA's Medical Devices Special Interest Group (MD-SIG) and a workshop leader.

**Dr Namrata Upadhyay** is a dental surgeon and a certified Clinical and Regulatory Medical Device professional. She is currently the Team Manager of Medical Writing and Safety Reporting at MD-Clinicals, Switzerland. She is also section editor of the EMWA *Medical Writing* journal and manages her free-lance business NamNR, where she provides MedComms services to the Medical Device and Pharma sector. She has authored multiple regulatory and clinical documents for all classes of medical CE devices and supports regulatory submissions for CE mark approval.





Nomenclature (EMDN), the designation of expert panels, the setting up of the Medical Device Coordination Group (MDCG) and its 13 subgroups, and other important work.

In order to address the serious challenges caused by the COVID-19 crisis as well as the situation related to the lack of notified bodies, notably under IVDR, the Commission also prepared amendments to the MDR and the IVDR concerning the dates of application of certain provisions and the related transitional regimes. This was necessary to take some pressure off national authorities, notified bodies, manufacturers and other actors coming from the handling of the COVID-19 crises and at the same time securing a smooth implementation of the new EU legislative framework for medical devices. The proposals were adopted within very speedy co-legislation procedures by the European Parliament and the Council.

As a necessary support to the legislative initiatives, to help all the interested parties to apply the MDR and the IVDR in practice, more than 90 guidance documents have been published following discussions and endorsement by the Medical Devices Coordination Group (MDCG), chaired and managed by the Commission (DG SANTE), with the participation of competent authorities and

stakeholders. Several other guidance documents and factsheets have been also developed and published directly by the Commission.

With respect to conformity assessment, the new Regulations strengthened the requirements and the procedures to designate notified bodies, including the participation of experts from Member States and the Commission in Joint Assessment Teams, to ensure adequate compliance. The number of notified bodies under the MDR and IVDR is continuously growing and they have increased their capacity and resources, but the situation is still challenging and more progress is needed.

It is worth mentioning also the international aspects related to the EU legislation on medical devices, to promote it to international partners and other jurisdictions, to ensure the same high level of protection of public health, as well as to facilitate exports for EU-based manufacturers. The related work includes the active representation of the Commission (DG SANTE) in the activities of the International Medical Device Regulators Forum (IMDRF) and the development and implementation of different types of international agreements with third countries in the field of medical devices.

A lot of work has been done so far, but there is still a lot of work to deliver in the next months

and years, to continue to successfully deal with all the challenges posed by the new EU regulatory framework for medical devices and avoid shortages of critical devices. Such challenges affect in different ways the relevant parties, including Member States, economic operators, conformity assessment bodies, patients, and users, as well as citizens in general. To jointly respond to these challenges, the European Commission services are always working and making all the best efforts to provide support, at the same time counting on the commitment and active participation of all the parties, to address a secure, smooth, and timely implementation of the regulatory framework.

#### Author information

**Ana Eva Ampelas** is Head of Unit for Medical Devices and Health Technology Assessment in the European Commission's Directorate-General for Health and Food Safety (DG SANTE).

**Mario Gabrielli Cossellu** is Legal and Policy Officer for Medical Devices in the same Unit.

# Incoming President's Message

**D**ear EMWA friends and colleagues, as I draft this message, we are coming to the close of EMWA's 53rd conference in Berlin, Germany. By all measures, it was a great conference with almost 400 delegates participating in our full programme comprising workshops, symposia, expert seminar series, other short seminars, and of course, the social events. What makes this conference special is that after 2 years of virtually "meeting", it was our first in-person, face-to-face conference under the new "normal". And the joy of seeing each other in the flesh was such a palpably honest and genuine emotion; we are truly social animals.

A lot has changed in the past 2 years, for some of us more than others. And yet, not only did our volunteers maintain our association's activities, but in fact we added to them. We showed a remarkable innovativeness and adaptability in organising conferences and bringing our widespread membership together, even if it was on the computer/mobile screens in our home

One of the major lessons of the COVID-19 pandemic is how critical scientific messaging is in order to curb the rampant 'infodemic' that has permeated all platforms for scientific and lay discourse, from social media to medical journals.

offices. For this, I would like to particularly thank the past three Presidents – Barbara Grossman, Beatrix Dörr, and Carola Krause – and the Executive Committee (EC) members for their stewardship as we traversed these unprecedented times. As I begin my tenure as EMWA President

for 2022-23, I would like to share with you that our association is in the best shape in its 30-year history, both financially and in terms of membership numbers. It is the result of the vision, perseverance, dedication, and teamwork of EMWA's volunteers, and it is an honour to be one of them.

At the first EC meeting of my presidency held during the conference, I had the opportunity to share with the team my goals for 2022-23. Of key importance is continuing to build awareness of medical writing as a profession and of EMWA and its outreach. EMWA's Ambassador Programme has been working on this for a few years; now that travel restrictions have been eased, it is time to ramp up the programme to reach

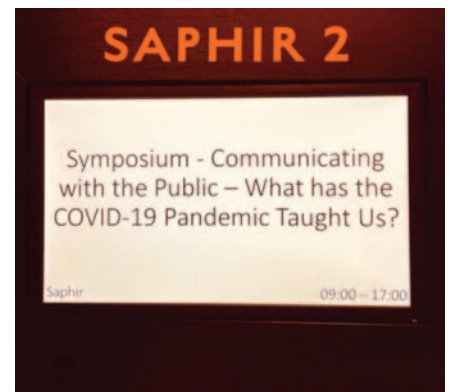
universities and career fairs and canvass for EMWA. In addition, we now also have the

Getting Into Medical Writing programme which seeks to inform fresh life science graduates on the various opportunities in medical writing and communications. Working in conjunction, it is my hope that we will see an uptick in EMWA membership over time.

Collaboration and teamwork being the bedrock of success, I am also keenly interested in furthering our partnership with organisations that are involved in activities similar to ours such as the American Medical Writers Association, the Australasian Medical Writers Association, the International Society for Medical Publication Professionals, and others. In this, we have a healthy history which has resulted in a number of key Joint Position Statements, one of the most

important being the one that establishes the role of professional medical writers in development of medical and scientific publications (<https://www.emwa.org/about-us/position-statements/joint-position-statement-for-professional-medical-writers/>). My goal is to strengthen our collaborative efforts with existing partners and reach out to others with similar aims.

One of the major lessons of the COVID-19 pandemic is how critical scientific messaging is in order to curb the rampant "infodemic" that has permeated all platforms for scientific and lay discourse, from social media to medical journals. With speakers representing stakeholders across the board – be it regulators, patient advocates, or medical professionals – our symposium at the conference was designed to specifically deal with this timely theme.



As medical communicators, I believe we occupy a key role in bridging medical and scientific information and public messaging. And the need of the hour is our active involvement. In order to promote this, I also plan to work closely with and support our Communicating with the Public Special Interest Group. Should you be interested in volunteering for this please contact me or the SIG Chairperson, Lisa Chamberlain James.

Finally, I would like to thank you for your continued involvement with EMWA.

Happy reading!



Satyen Shenoy

EMWA President 2022-23



# Outgoing President's Message

**D**ear friends, colleagues, and EMWA members, despite the global COVID-19 pandemic and the war in the Ukraine, EMWA's financial situation and membership numbers remained stable over my term of presidency. In fact, membership numbers slightly increased from 2021, and we are happy to welcome 20 new EMWA members this year. With the newly introduced concept of hybrid conferences, EMWA was able to support and engage our members on the new advances in the industry over the past years.

To provide year-long learning and engagements, several new working groups were established during my presidency (see EMWA's organigram):

- Communicating with the Public Special Interest Group (CwP SIG)
- Business Development Special Interest Group (BD SIG)
- Getting into Medical Writing (GiMW)
- EMWA's Creative Team (CT)
- Salary and Compensation Survey Team (SCST)
- EMWA Advisory Board (AB)

For further details, please see the president's report in the Annual Meeting (AM) report 2021-2022.

All of the above initiatives would not have been possible without the continuous effort and commitment from our members, our volunteers, and Head Office. I believe I have never shared so much joy and sorrow with a group of people. Debra, Claire, Carrie, Tracey, Candi, and Amy – kudos to all of you.

I have the uttermost respect for my Executive Committee colleagues Satyen Shenoy, Somsuvro Basu, Sarah Choudhury, Marian Hodges, Maria João Almeida, Raquel Billiones, Diarmuid De Faoite, and Slávka Baróniková. We went through a number of controversial discussions but always treated each other with respect and lived up to the EMWA spirit. Because of our multicultural backgrounds, we were able to approach problems from very different angles which, in the end, guaranteed continuity for EMWA during these challenging times.

As Diarmuid De Faoite and Marian Hodges step down from their EMWA commitments, I would like to thank both for

their long-term support. Both have shaped the organisation in many ways.

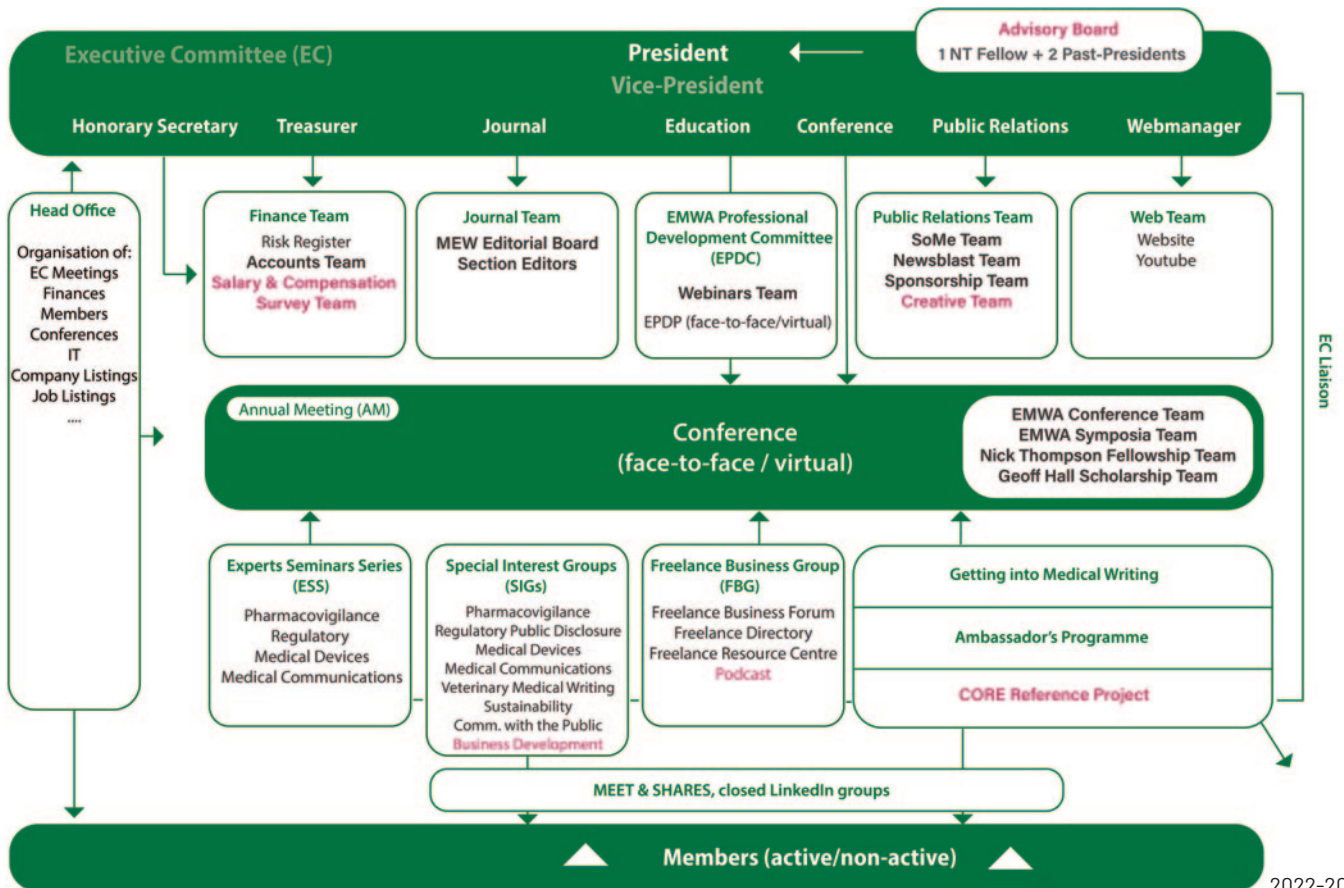
Thank you for your continuous commitment to the EMWA!

I am convinced that under the leadership of Satyen Shenoy (EMWA President 2022-2023) and Maria Kołtowska-Hägström (EMWA Vice President 2022-2023), the newly elected and appointed EC members (elected: Jules Kovacevic and Laura Collada Ali [Education Officers, co-chairing]; appointed: Allison Kirsop [website manager]) will lead EMWA into an exciting post-pandemic era.

Thank you for the exciting opportunity to lead EMWA from May 2021 to 2022.



**Carola Krause**  
EMWA President 2021-2022



2022-2023

# From the Editor

## EMWA 30 years and 53 conferences later

**E**MWA celebrates its 30th anniversary this year. For someone like me born in the 60s long before the moon landing, 30 seems a pretty young age. But if we look at some of the institutions born in the 90s, EMWA is actually in good company.

EMWA predates the European Union (EU), which was officially formed in November 1993 in Maastricht, the Netherlands. Over a year later, the European Medicines Agency opened shop in January 1995.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), on the other hand, founded in 1990, is 2 years older.

The 90s also marked a quantum leap in technology. In those days, the terms “virtual” and “online” were not commonly used, and there were no “Apps” and “SoMe”. But the use of the internet and personal computers started to become popular.

In digging through our paper archives the other day, I stumbled upon volumes of journals and conference proceedings from the 90s, from the days when my husband (a computer scientist) and I were still PhD students. One of his papers was about a “cutting edge” platform called hypermedia system for conference

organisation (HMSCO), presented at the 1995 Education and Multimedia Annual Meeting (ED-MEDIA 95) in Graz, Austria. The publication was about harnessing the internet in organising a conference from start to finish. The high level headings of the paper are:

- Invitation and call for contributions
- Submission and review of contributions
- Registration and event preparation
- The conference event itself
- Presentations
- Scientific exchange and communication
- Social and non-scientific matters
- Post-event matters

Reads familiar? This could easily be a checklist from the last 3 virtual EMWA conferences. Through technology that started approximately 30 years ago, EMWA braved the pandemic months from 2020 to 2021, continued to serve its members through virtual educational offerings and networking events – and this journal.

The 53rd EMWA conference in Berlin will forever be remembered as the 30th anniversary gathering of medical writers and communicators in postpandemic Europe. It was fun but



**Raquel Billiones**  
Editor-in-Chief  
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poignant, exhilarating yet humbling.

To conclude this editorial, I would like share this direct quote from the same paper:

*“The main ideas behind the HMSCO are to further reduce manual work by automating repetitive tasks, to support participants and organisers at the event itself, to simplify communication, to enhance availability of resources, and to speed up the transfer of information and data.*

*However, the future of conferences will certainly not be all hypermedia... HMSCOs are mainly intended to aid people to meet each other, not to hold meetings in cyberspace. Conferences in the current form [in person] will remain absolutely essential and necessary. Nothing will ever replace the personal contact and the verbal, direct communication between researchers...”*

I fully agree. Technology advances, viruses mutate, but humans will always be social animals. Here’s to EMWA’s next 30 years.



**EMWA Editorial Board members (L-R) Evgenia Alechine, Raquel Billiones, Phil Leventhal, and Jonathan Pitt at the May EMWA conference in Berlin, Germany.**

# Berlin

## Conference Report



The European Medical Writers Association (EMWA) hosted its first in-person conference in 2 years on May 3 to May 7 in Germany's beautiful capital of Berlin.

Nearly 400 delegates attended for four days of workshops, symposia, seminars, and (of course) networking and social events, including a banquet celebration of EMWA's 30th Anniversary. Other activities included conversation over coffee and walking tours throughout the city, including to the Berlin Wall.

"Through technology, EMWA continued to serve its members through virtual educational offerings and networking events during the pandemic. Virtual conferences are here to stay but nothing will ever replace the personal contact and the verbal, direct communication between colleagues and friends in face to face events," said Raquel Billiones, editor-in-chief of *Medical Writing*.

Looking forward to seeing you all again soon at our next conference

## Riga, Latvia

November 3 - 5  
Registration opens in September





## Executive Committee election 2022

We are excited to announce that the results are in, and you have elected your new Executive Committee members! We value your support. Huge congratulations to the new EC members!

- **Maria Kołtowska-Häggström** – Vice President
- **Slávka Baróniková** – Conference Director
- **Laura C Collada Ali** and **Jules Kovacevic** – Education Officer (job share)

We are happy to inform you that **Allison Kirsop** is our new Website Manager (the Website Manager and the EMWA Journal Editor are both appointed positions and are members of the Executive Committee). Welcome, Allison!



Carola Krause and  
Jocelyne Basseal

## EMWA to participate in developing document standards for medical devices

In late 2021 an expert group was set up in the UK to create a horizontal standard for clinical evaluation. The group includes representatives from a regulatory authority, a notified body, EMWA, a trade association, and from some medical device manufacturers and consultancies. It is intended that the draft standard will be developed into an ISO standard on clinical evaluation of medical devices by an ISO working group. It is not yet known when this standard will be available, but it is eagerly awaited by those working in medical devices.

– Gillian Pritchard

## The beginning: EMWA & AMWA (Australasian Medical Writers Association)

Outgoing EMWA President **Carola Krause** met her **AMWA** counterpart **Jocelyne Basseal** in Sydney on April 22, 2022 – as an initial step to strengthen our partnership. This co-operation will create opportunities for education and future global position statements benefitting the medical writing community and the members of both associations.

We congratulate AMWA on its 40th anniversary and look ahead to a fruitful alliance!

### Did you know?

Existing EMWA members can receive a 10% discount off their next year's EMWA subscription for referring a new member to EMWA.

For more information, please contact Head Office at [info@emwa.org](mailto:info@emwa.org).

## ONE YEAR MEMBERSHIP

### Gift Card



EUROPEAN MEDICAL WRITERS ASSOCIATION

### Membership gift card

You can now offer a 1-year membership gift card to a friend! For more information, email [info@emwa.org](mailto:info@emwa.org).



### EMWA Membership Hardship Fund

Would you like to remain or become an EMWA member again but are unable to because of financial difficulties and facing tough times?

If so, EMWA would like to provide you with some assistance.

To be considered, you must be an existing or past EMWA member. There is no limit to the number of applications; the Treasurer, with support from the EMWA Executive Committee (EC), will review them. Each application is judged on a case-by-case basis. We request 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 can – and the rest, EMWA will cover. If you cannot contribute at all, EMWA will not discriminate.

If you qualify, we will then review your case again every year. 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. Please email for further information or apply at [info@emwa.org](mailto:info@emwa.org).

### EMWA Finance Committee and the Salary & Compensation Survey Team: We need you!

We need volunteers! Come and join the EMWA **Finance Committee**\*! If you have a head for figures and budgets and can help to ensure that EMWA's membership funds are well spent, please apply!

The Finance Committee currently has 6 existing members, including the Treasurer and the Honorary Secretary. Email updates are sent quarterly, and we meet (virtually) on an ad-hoc basis (depending on need and availability). We need more volunteers!

The **Salary & Compensation Survey Team** meets and conducts the **EMWA Salary Survey** every 4 to 5 years for the EMWA members to help track the current compensation trends for medical writers. The aim is to present updates to EMWA members at EMWA conferences and ultimately prepare for publication in *Medical Writing*.

We are a not-for-profit organisation, run by its members and for its members. Your support would be much appreciated. Depending on the level of involvement, volunteers may qualify under the volunteer reimbursement policy.

Please email [treasurer@emwa.org](mailto:treasurer@emwa.org) and/or [salaryandcompensationsurvey@emwa.org](mailto:salaryandcompensationsurvey@emwa.org) for further information, or apply at [info@emwa.org](mailto:info@emwa.org). *\*The Finance Committee and the Salary and Compensation Survey Team are headed up by the Treasurer, and EMWA finances are overseen by Head Office's accountancy department.*



### Ambassadors Programme News

The EMWA Ambassador Programme is continuing its efforts to reach out to new audiences to promote medical writing and EMWA.

**Anne McDonough** gave a virtual presentation on careers in medical writing combined with a workshop on improving writing skills at University College London Life Sciences Careers Week on March 10, 2022. Altogether there were 59 online participants who had many interesting questions on how to get experience in medical writing and writing publications.

On March 22, 2022, outgoing EMWA President **Carola Krause** gave a presentation on writing the Investigational Medicinal Product

Dossier (IMPD) to an audience of researchers at the **SPARK-BIH Educational Forum**. The SPARK-BIH programme is designed to teach academic scholars the principles of Drug, Device & Diagnostic Development, focusing on topics relevant to translational medicine. Carola was joined by **Abe Shevack**, who introduced the audience to medical writing and EMWA.

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

# Differences between writing for medical devices and pharmaceuticals: An update

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## Abstract

Although the medical device and pharmaceutical industries are related, they are governed by distinct regulatory systems. Despite the similarities, the inherent differences between medical devices and drugs have implications for clinical research and medical writing. There has been a recent move to adopt more stringent regulatory requirements for the medical device industry, bringing the environment closer to what we have come to expect from the highly regulated pharmaceutical industry. The present article is a follow-up to a previous article published in *Medical Writing* in 2017, which introduced writing for medical devices and the challenges for medical writers coming from a pharmaceutical regulatory environment. In this article, we present our current knowledge about authoring documents for medical devices, the parallels with the pharmaceutical regulatory system, and the essential guidance documents.

**A**lthough the medical device and pharmaceutical industries seem intrinsically related, they are governed by distinct regulatory systems. An article published in *Medical Writing* by Beatrix Doerr and colleagues in 2017<sup>1</sup> discussed the inherent differences between drugs and medical devices and their implications for clinical research and medical writing in general. The article also noted parallels between the different phases of clinical trials for pharmaceutical drugs and studies assessing the feasibility, safety, and performance of medical devices (Table 1). The article served as a good introduction to the similarities and differences between the two regulatory environments, and it forewarned the move towards the more stringent

regulatory environment that has governed medical devices since.

The pharmaceutical industry has long had the benefit of International Council for Harmonisation guidelines,<sup>3</sup> the CORE Reference manual,<sup>4</sup> and well-established, accessible document templates.<sup>5</sup> By comparison, the medical device regulatory environment is relatively young and not as well structured. In fact, medical writers with a pharmaceutical background may feel that the medical device regulatory environment only recently started to catch up with the clinical regulatory environment. The structural differences between the two regulatory environments were particularly evident in the early days of medical device trials and documentation, especially before the implementation of the European Union Medical Device Regulation (MDR) 2017/45 (see Table 2 for a list of key medical device-related terms and definitions).<sup>6</sup> However, with increasing experience, and as guidance documents and position papers have been published by the notified bodies, the medical

device industry is becoming more structured and specific. This has inevitably made writing for medical devices more attractive for medical writers.

## Guidance documents for medical device writing

As part of the transition from Medical Device Directive (MDD) 93/42/EEC to MDR in 2021,

the previous guidance documents (“MEDDEVs”) have gradually been replaced by newer ones issued by the European Commission and endorsed by the Medical Device Coordination Group (MDCG). These are aimed at providing a uniform application and interpretation of the MDR within the European Union.<sup>7</sup> Although not legally binding, the MDCG guidelines

Although not legally binding, the MDCG guidelines are considered to be the official interpretation of the MDR.

are considered to be the official interpretation of the MDR, and they will help move towards implementation of MDR Article 105 and the “effective and harmonised implementation of the Regulation”.

Like the MEDDEVs preceding them, the MDCG guidelines are broad and cover several

**Table 1. Clinical studies for pharmaceuticals and medical devices**

Pharmaceutical clinical study phase	Equivalent in medical device study	
	Pre-market	Post-market
Phase I	Pilot study <ul style="list-style-type: none"> <li>• first in human clinical investigation</li> <li>• early feasibility clinical investigation</li> </ul>	
Phase II	Pivotal study pivotal clinical investigation	
Phase III	Pivotal study pivotal clinical investigation	Post-market clinical investigation
Phase IV		Registry Observational study Real world data collection

Adapted from Doerr et al. (2017)<sup>1</sup> and ISO 14155 Annex L.<sup>2</sup>



topics, including classification of devices, clinical investigations, clinical evaluation, clinical evidence, post-market activities, and in vitro diagnostics. As of January 2022, 11 MDCG guidance documents were listed on the European Commission website as relevant to clinical investigations and evaluations.<sup>7</sup> Other guidance documents should be issued later in 2022, some of which will discuss post-market surveillance, vigilance, and Periodic Safety Update Report (PSUR) requirements under the MDR. Familiarisation with these guidance documents is thus important for the medical writer involved in writing for medical devices. Some of the guidance documents are discussed in Table 3.

### A closer look at the documents required for drugs and medical devices

Although the regulatory environments for the early stages of clinical trial and medical device investigations are similar, differences start to become more pronounced once at the point of entry on the market. Table 4 lists some of the documents required for pharmaceutical products and medical devices throughout the various stages of the product lifecycle.

#### Documents for clinical trials and investigations

In the MDR, clinical trials are referred to as “clinical investigations” (Articles 2 (45), 62–82;

Annex XV).<sup>6</sup> The requirements in the MDR regarding clinical investigations are based on BS EN ISO 14155:2011 (updated in 2020).<sup>2</sup> The MDR goes into much more detail than the MDD regarding clinical investigations. Specifically, Articles 62 through 80 of the MDR address:<sup>6</sup>

- General requirements regarding clinical investigations conducted to demonstrate conformity of devices
- Informed consent
- Clinical investigations on subjects requiring special consideration
- Application process and assessment by member states
- Conduct of the clinical investigation
- Electronic system on clinical investigations and other aspects

Clinical investigations to demonstrate conformity of devices (Article 62) can be considered pivotal clinical trials conducted to prove the intended performance, clinical benefits, and clinical safety of an investigational device. The MDR specifically states that pivotal clinical trials shall be performed in “a clinical environment that is representative of the intended normal conditions of use of the device in the target patient population” (Annex XV). The MDR does not, however, favour or specify particular trial designs but rather applies the principle of proportionality and a risk-based approach (see

also ISO 14155:2020, Annex I).<sup>2</sup>

Required documentation includes a Clinical Investigation Plan (analogous to the Clinical Study Protocol in pharmaceutical trials), which must address safety for patients and users (see MDR Articles 2, 62, 72).<sup>6</sup> The requirements stated in MEDDEV 2.7.1/4 for the Clinical Investigation Plan are still relevant: the document must state the rationale, objectives, design, and proposed analysis, methodology, monitoring, conduct, and record-keeping of the clinical investigation.<sup>8</sup>

Similar to drug trials, medical device clinical investigations require informed consent in line with ISO 14155 and the Declaration of Helsinki (see MDR Article 63). The informed consent form should highlight and state potential risks, benefits, and treatment options, and it should contain information about the trial conduct in a language that is easily understood by the participants. This might require an additional “readability assessment” aimed at providing a document that can be easily understood by laypersons and the potential study population.

As for clinical trials, an Investigator Brochure is required for medical device investigations. It should contain clinical and non-clinical information on the investigational device relevant to the investigation and should be available at the time of application (MDR Annex XV, Chapter II).<sup>6</sup>

**Table 2. Key medical device-related terms and definitions**

Term	Abbreviation or acronym	Definition
Conformité Européenne mark	CE mark	Marking on a product to signify that it meets the legal requirements to be sold on the extended Single Market in the European Economic Area (EEA).
Clinical Evaluation Plan	CEP	The CEP can be considered as the road map for conducting a clinical evaluation process. It includes the scope, methodology and systematic approaches that will be used during the clinical evaluation, which will be documented in a CER. The CEP will identify the route for conformity as well as any clinical benchmarks and specific measurable outcomes for both clinical safety and performance.
Clinical Evaluation Report	CER	A document that collates all data proving the intended purpose of a device, its target groups, and its clinical benefits, along with the indications and contraindications. The CER will demonstrate safety and performance as well as the overall positive benefit-to-risk-ratio for a medical device through critical evaluation of all available data. A CER is required to show that a medical device is compliant to the Essential Requirements of the MDD/General Safety and Performance Requirements of the MDR.
Clinical Investigation Plan	CIP	A document that includes details on the rationale, aims, objectives, design, and proposed methodology and analyses of a clinical investigation of a medical device.
Clarity and Openness in Reporting: E3-based	CORE	The CORE Reference is a user manual to help medical writers navigate relevant guidelines as they create content for clinical study reports.
European Databank on Medical Devices	EUDAMED	A secure, central, web-based portal for the exchange of information between national Competent Authorities and the European Commission. Under the MDR, this will be interoperable and publicly accessible. The new database is designed to be multifunctional, i.e. a registration, collaboration and notification system.
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	ICH	The ICH is an initiative that brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration.
Medical Device Coordination Group	MDCG	The MDCG advises and assists the European Commission and Member States in ensuring a harmonised implementation of the new EU MDR. The Group publishes legally non-binding guidance documents in accordance with Article 105 of Regulation 745/2017 to help ensure uniform application of the relevant regulations within the EU.
Medical Device Directive	MDD (93/42/EEC)	The MDD (Council Directive 93/42/EEC) came into force in 1993 with the aim of harmonising the laws relating to medical devices within the EU. In order for a manufacturer to legally place a medical device on the extended EU Single Market (i.e. have the CE mark applied), the requirements of the MDD had to be met. This has been replaced by the EU MDR which comes into force in May 2020.
Medical Device Regulation	MDR 2017/745	The EU MDR is a set of regulations that govern the clinical investigation, production and distribution of medical devices in the European Union. Compliance with this regulation is mandatory for medical device companies that want to sell their products in the European marketplace. The EU MDR replaces the previous Medical Device Directive (MDD) and Active Implantable Medical Devices Directive 90/385/EEC (AIMDD). Under the new medical device regulation, manufacturers need to provide more in-depth clinical data to demonstrate their safety and performance claims.
Revision 4 of the Clinical Evaluation Guidance Document MEDDEV 2.7.1	MEDDEV 2.7/1 rev. 4	A document that provides guidance for medical device manufacturers and notified bodies who must perform clinical evaluations for medical devices that fall under the MDD (93/42/EEC) and AIMD (90/385/EEC). This document, along with the MDR, forms the basis for clinical evaluation of a medical device. CE certifications under MDD were historically based only on product equivalency. The MEDDEV 2.7/1 rev. 4 and MDR now substantially tighten the requirements for equivalence justification compared to before.



The content of the clinical investigation report is described in ISO 14155:2020,<sup>2</sup> and the minimum requirements can be found in Chapter III point 7 of Annex XV of the MDR. Further guidance can be found in MDCG 2021-6.<sup>9</sup> The guidance documents MDCG 2020-10/1 (Safety reporting in clinical investigations of medical devices under the Regulation EU 2017/745)<sup>10</sup> and MDCG 2020-10/2 (Clinical Investigation Summary Safety Report Form v1.0)<sup>11</sup> are available on the European Commission website.

### Trial disclosure and publications

Reporting of clinical results is discussed in the MDR Article 77. For clinical investigations carried out for conformity purposes (MDR Article 62) or for CE (*Conformité Européenne*)-

marked medical devices (MDR Article 74), a clinical investigation report and summary should be submitted to all Member States in which a clinical investigation was conducted within 1 year of the end of the clinical investigation, although later may be justified for scientific reasons and specified in the Clinical Investigational Plan. In cases where the clinical investigation is terminated early or halted temporarily, publication of results should occur within 3 months. Study sponsors are expected to submit a risk analysis addressing any safety issues related to the temporary halt. The report and lay summary should become publicly available:

- Immediately after submission in cases of early termination or temporary halt.
- When the medical device is registered

(Article 29) and before it is placed on the market.

- At the latest 1 year after submission of the report and summary if it is not registered before that time.

MDCG 2021-6 further details the requirements and timelines for reporting of clinical investigations.<sup>9</sup>

### Common Technical Documents vs. Technical Documentation

For pharmaceutical products, the Common Technical Document was designed to provide a common format for the technical documentation included in an application for the registration of a human pharmaceutical product.<sup>12</sup> In essence, it

Table 2. continued

Term	Abbreviation or acronym	Definition
Post-market clinical follow-up	PMCF	This is a specific form of post-market surveillance that is required for devices of Class IIb and higher. The PMCF includes all clinical evidence such as literature publication on safety and performance as well as use and adverse events reports that should be gathered as part of post-market surveillance for all medical devices on a periodic basis.
Post-market surveillance	PMS	The MDR defines PMS as a proactive and systematic process that manufacturers must implement in order to take corrective and preventive action in accordance with information on medical devices and their performance. A PMS system should be used to actively gather and analyse data on the quality, performance, and safety of the device throughout its lifetime. The PMS should result in a PMS plan the results of the plan should generate a report.
Periodic Safety Update Report	PSUR	The PSUR is essentially an extension of a post-market surveillance report that is required only for moderate and high-risk devices (Class IIa, IIb, III, implantables). It summarises the results and conclusions from PMS data, provides a summary of post-market information, vigilance reporting, and current status of these devices on the market in the EU and a rationale and description of any corrective actions taken for product on the market. This is a new demand placed upon all manufacturers by the MDR. The PSURs are required at least every year for class III devices and class IIb implantable devices and at least every 2 years for class IIa devices and class IIb non-implantable devices.
Summary of Safety and Clinical Performance	SSCP	The SSCP is an important MDR requirement that is tied to PMCF activities for implantable and class III medical devices. The SSCP is intended to provide healthcare practitioners and relevant patients access to current clinical data and other information about the safety and clinical performance of the medical device. The SSCP needs to be updated when the PMCF and PSUR are updated as part of the ongoing lifecycle of these regulatory documents. The specific requirements of the SSCP can be found in Article 32 of the MDR, with further guidance released in MDCG 2019-9.
Technical document	TD	TD is a generic term for product documentation outlining the general safety and performance requirements of a medical device as evidence of conformity with the relevant legislation. The MDR provides a clear structure of the technical documentation required by manufacturers. In case of Class I self-certified products, technical documents are not always subject to review while in the case of Class I non-sterile up to Class III, the Technical Document is always subject to a review by the notified body.

**Table 3. List of guidance documents to be considered during the clinical evaluation process**

Guidance document	Description
EU MDR 2017/45 Article 61	Article 61 discusses clinical evaluation and the need for clinical investigations. Clinical investigations shall be performed for novel implantable and Class III medical devices to demonstrate that the device is compliant with the GSPRs set out in Annex I of the MDR. Article 61.6(a) also states that for a device cleared under the MDD with sufficient clinical data, it is not required to conduct a clinical investigation. A list of exempt devices is also provided in Art 61.6 (b).
MDCG 2019-9 Summary of safety and clinical performance	For Class III and implantable devices. Provides definition and templates.
MDCG 2019-11 Software as a medical device	MDCG 2019-11 is the guidance document that addresses medical device classification and includes software as a medical device.
MDCG 2020-5 Guidance on clinical evaluation – Equivalence	Covers equivalence in clinical evaluations. Defines technical, biological, and clinical requirements that need to be addressed when claiming equivalence to an already established device.
MDCG 2020-6 Guidance on sufficient clinical evidence for legacy devices	Defines “sufficient” clinical data for legacy devices and well-established technologies. Provides a hierarchy of clinical evidence (Appendix III) Also defines important terms such as: indication/indication for use; intended purpose/intended use;state of the art
MDCG 2020-7 Post-Market Clinical Follow-up Plan MDCG 2020-8 Post-Market Clinical Follow-up Report	The MDCG 2020-7 provides a template for the post-market clinical follow-up plan, while MDCG 2020-8 provides a template for the report. The MDR requires continuous post-market clinical follow-up activities, which will feed back and impact the Clinical Evaluation Report, Periodic Safety Update Report, and Summary of Safety and Clinical Performance, if relevant.
MDCG 2020-13 Clinical evaluation assessment report template	This is a document aimed at notified bodies, but manufacturers and writers should be familiar with the document as it defines what minimum amount of information will be sought by the notified bodies. There is also information on best practices for conducting literature searches
MDCG 2021-24 Guidance on Classification of medical devices	This guidance has brought about some further definitions and changes that particularly affect Class IIb implantable devices and spinal devices, which have now been up-classed to Class III.
International Medical Device Regulators Forum	IMDRF is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force on Medical Devices and aims to accelerate international medical device regulatory harmonization and convergence. IMDRF provides working groups for specific topics (e.g., IVD medical devices, AI devices, adverse event terminology), support for documents, and even consultations.

is divided into five main modules:

- Module 1 – Administrative information and prescribing information
- Module 2 – Overviews and summaries of Modules 3–5
- Module 3 – Quality (pharmaceutical documentation)
- Module 4 – Non-clinical reports (pharmacology/toxicology)
- Module 5 – Clinical study reports (clinical trials)

Similarly, for medical devices, a Technical Document (TD) is required. The TD includes all the documentation providing evidence and supporting compliance with the general safety and performance requirements of the MDR (Annex I). The TD represents the entirety of the documents describing a device and includes the device’s design, development, verification & validation (including clinical and performance validation), along with its regulatory status within target markets. Furthermore, the MDR now requires a closed-loop process, implemented with

data from the post-market use of the device, to ensure that early warnings are captured, that the “General Safety and Performance Requirements” are continuously fulfilled, and that the benefits for the patient always outweigh the risks. The TD must be made available for all devices irrespective of device class and before placing a medical device on the European market, as it provides evidence of conformity with the relevant legislation.

In contrast to the MDD, the MDR Annex II and Annex II define the requirements and specify

criteria for the TD on post-market surveillance (Table 5).<sup>6</sup> Medical writers may occasionally be asked to assist in updating technical documentation in compliance with the MDR.

Most writers working in the medical device industry will have been involved in regularly updating Clinical Evaluation Plans and Clinical Evaluation Reports to meet and maintain MDR compliance. These documents are based on the TD. Depending upon the class of device, other documents may be required.<sup>13</sup> The clinical evaluation process aims to establish whether a CE-marked device meets the relevant general safety and performance requirements throughout its expected lifetime. The clinical evaluation process will draw conclusions about the clinical safety and performance of the device, with a focus on comparing its benefit-risk balance with the current state of the art.

Of note, starting May 26, 2024, all devices placed on the market must be in conformity with the MDR. MDD devices already on the market may continue to be made available until May 27, 2025. With deadlines fast approaching, medical device manufacturers have been increasingly requesting updates to their TDs and their Clinical Evaluation Plans and Clinical Evaluation Reports.

### Documents related to pharmacovigilance, post-market surveillance and safety reporting

The MDR not only mandates post-marketing surveillance for all devices but also introduces new and expanded requirements that increase compliance efforts. Annex III of the MDR 2017/745 details the European Union requirements. Manufacturers of low-risk Class I devices must create a post-market surveillance report, while manufacturers of Class IIa, IIb, and III devices must submit a PSUR.

Moreover, manufacturers must prove that Post-Market Clinical Follow-Up (PMCF) plans have been carried out for their medical devices or provide a justification if it is omitted. The PMCF is one component of the post-market surveillance (PMS) activities and is required depending on the device's risk and novelty. Devices designated as high risk or first of their kind require a PMCF. Traditionally,

Although regulatory guidance for pharmaceuticals has been well established and structured for some time, the guidance for medical devices is relatively young and unstructured.

PMS activities for medical device relied on reactive data gathering, but with the advent of the MDR, manufacturers are expected to take a more proactive approach to data collection and feedback of results into design, clinical evaluation, and technical documentation, with the intent of using real-time data to anticipate risks.

### Documents and information aimed at patients and users

Article 32 of the MDR introduces a requirement for a Summary of

Safety and Clinical Performance (SSCP) for implantable device and Class III devices not custom-made or investigational. The SSCP is intended to provide an objective summary of the results obtained from the clinical evaluation. It should be seen not as a replacement to the Instructions for Use but rather as a supplement describing the end user of the device, whether they are healthcare professionals or patients, and the essential information related to the device.<sup>14</sup>

Information written for patients is mandatory for implantable devices for which patients will be given implant cards and for Class III devices intended to be used directly by patients. The SSCP will be available in the



**Table 4. Documents within the lifespan of pharmaceutical products and medical devices**

Document type	Pharmaceutical products	Medical devices
Study protocol	<b>Clinical study protocol</b> Including all information deemed necessary to conduct a clinical trial with pharmaceuticals (see ICH E6 Section 6)	<b>Clinical investigation plan</b> Equivalent document to pharmaceuticals with specific focus on safety not only for patients, but also for users (see EU MDR Article 2, 62, 72)
Informed consent	<b>Informed consent form</b> Stating all risks, benefits, treatment options, contains information about the trial conduct in lay language that all trial subjects have to date and sign themselves or a legal representative for e.g., minors, ICFs have to be updated in case of new trial findings that impact the risk/benefit evaluation (see ICH E6 Section 4.8)	<b>Informed consent</b> Medical device trial also requires a form as in pharmaceutical trials (as per EU MDR Article 63, follows the same principles as pharmaceuticals, i.e., the Declaration of Helsinki)
Investigator's brochure (IB)	The IB is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects (see ICH E6 Section 7).	The IB shall contain the clinical and non-clinical information on the investigational device that is relevant for the investigation and available at the time of application (see EU MDR Annex XV, Chapter II, content guidance also found in ISO 14155 Annex B).
Study report	Clinical study report – according to CORE and/or ICH E3 reports all outcomes and results from a clinical trial	Clinical Investigation Report – the content of the study report is described in ISO 14155:2020 and the minimum requirements can be found in Chapter III point 7 of Annex XV of the EU MDR; further guidance – MDCG 2021-6.
Patient information	<b>PIL, information sheets, etc.</b> ICH E6 does not state the form of patient information, other than the content of the ICF (see above)	Patient information is not directly described in the EU MDR. MDCG 2019-09 clearly states the Summary of Safety and Clinical Performance (SSCP) as a source for patient's information (see below) For implantable devices, the necessity of an implant card and information to be supplied to the patient is described in EU MDR, Article 18
Update reports	<b>Periodic Safety Update Report, PSUR</b> The study sponsor is required to submit regular safety update reports (see ICH E6 Section 5)	<b>PSUR</b> Manufacturers of class IIa, class IIb and class III devices shall prepare a PSUR for each device (see UE MDR Article 86). A finalised guidance for device PSURs is still outstanding, but an MDCG guidelines is expected sometime in 2022.
Results and clinical trial publication/s	Basic results must be posted 12 months after the date of last patient visit on <a href="http://clinicaltrials.gov">clinicaltrials.gov</a>  There may be more than one publication arising from a clinical trial.  Patient data must be protected/redacted. High level clinical trial publications are common courtesy.  Regulation (EU) No. 536/2014 on clinical trials on human medicines (the Clinical Trials Regulation) provides a legal basis for the release of clinical trial results conducted in the EU and authorised under this Regulation. It entered into application on January 31, 2022.	The EU MDR states that the publication of study results shall be done in accordance with recognized ethical principles (see Annex XV Chapter I)  Reporting of clinical results is discussed in the EU MDR Article 77  In general, publications of medical device trials are usually less rigorous designs and have lower level of evidence.

Table 4. continued

Document type	Pharmaceutical products	Medical devices
(Post-) Market access documents	<p><b>CTD modules</b></p> <p>The Common Technical Document (CTD) contains 5 modules, whereas module 1 is not part of the CTD and entails regional administrative information. Module 2 is built up by summary and overview documentation. Module 3 contains the quality documentation, module 4 the non-clinical study reports, and module 5 all clinical study report about the investigational drug in question.</p>	<p><b>Technical documentation (also technical file)</b></p> <p>Contains all descriptions, documentation, classification, SSCP, labelling documents, GSPR evidence, about risks and benefits, pre-clinical and clinical evidence, the so-called Product verification, and validation, and as part of it the clinical evaluation and PMS with documents listed below, that might be of particular interest for medical writers:</p> <p><b>CEP</b></p> <p>Clinical evaluation plan (see Annex XIV Part A)</p> <p><b>Systematic literature review</b></p> <p>As per EU MDR Article 61, the systematic literature review is a procedural step of the clinical evaluation. There is no comparable methodological equivalent requirement for pharmaceuticals. Depending on the manufacturer's needs, the state-of-the-art literature review can lead to a stand-alone document, embedded in the clinical evaluation. The review and appraisal of clinical literature of not only the device under evaluation but also of the benchmark devices often presents as one of the major tasks for medical writers.</p> <p><b>Clinical evaluation report</b> (see Annex XIV Part A)</p> <p>Summarises all information deemed necessary for market access or prolongment. Contains information from PMS, PMCF, Risk Management File, Instructions for Use, and other source documents (Medical writers are usually not involved in the preparation of those source documents but can be asked to assist).</p> <p><b>Summary of safety and clinical performance</b> document intended to provide public access to an updated summary of clinical data and other information about the safety and clinical performance of the medical device (for guidance see MDCG 2019-9). Translations necessary for all languages where medical device is marketed.</p> <p><b>Instructions for Use</b> – Technical document describing all information for the use of the device, including all precautions, warnings, and risks for both patients and users. (Medical writers may assist in writing Instructions for Use). Some of the content may resemble the setting of an SmPC (summary of product characteristics) for pharmaceuticals.</p>

Table 5. Content required for Technical Documents per MDR Annex II &amp; Annex III

Document	Required content
Annex II – Technical Documentation	<ol style="list-style-type: none"> <li>1. Device description and specification, including variants and accessories Device description and specification 1.2 Reference to previous and similar generations of the device</li> <li>2. Information to be supplied by the manufacturer</li> <li>3. Design and manufacturing information</li> <li>4. General safety and performance requirements (GSPRs)</li> <li>5. Benefit–risk analysis and risk management</li> <li>6. Product verification and validation <ol style="list-style-type: none"> <li>6.1 Pre-clinical and clinical data</li> <li>6.2 Additional information required in specific cases</li> </ol> </li> </ol>
Annex III – Technical Documentation on Post-market Surveillance (PMS)	<ol style="list-style-type: none"> <li>1. The post-market surveillance plan</li> <li>2. The PSUR (Periodic Safety Update Report)</li> <li>3. PMS Report</li> </ol>

public domain and will eventually be available on the EUDAMED database of medical device. This introduces new challenges for manufacturers and medical writers because the documents will be more closely scrutinized. Moreover, the medical writer will need to write these documents with the intended user in mind and eliminate potentially confusing medical jargon.

## Conclusion

Although regulatory guidance for pharmaceuticals has been well established and structured for some time, the guidance for medical devices is relatively young and unstructured. Medical writers need to be aware of the similarities and differences between regulatory documents for pharmaceuticals and medical devices. Guidance documents and feedback provided by notified bodies has been crucial in providing clarity to this field. A number of MDCG guidelines are to be issued this year, and medical writers will be expected to familiarise themselves with these new updates and interpretations of the MDR. Writers in the field of medical devices should also be on the lookout for position papers issued periodically by notified bodies that can shed further light on the grey areas of the medical device regulations.

The move towards a more structured medical regulatory environment and the increasingly detailed device documentation required by the MDR have brought about a number of challenges. However, this has also proved to be attractive to medical writers looking to work in a more fast-paced, technical environment. Luckily, demand is not expected to slow for skilled medical writers who can assist in compiling medical device technical documentation and who have sufficient clinical experience to

produce sound reports for clinical evaluation and post-market activities.

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## Disclaimers

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

## Disclosures and conflicts of interest

The authors declare no conflicts of interest.

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# Implantable medical devices:

## Preclinical testing in new product development – On the road to clinical reality

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### Abstract

Implantable medical devices (IMDs) have restored viable and meaningful lives to millions of people who would have otherwise continued to be severely restricted or suffered early death due to their pathologies. Research and development of IMDs are complex and time-consuming and market authorisation is regulated by country laws and regional regulations to provide safe, effective, and reliable products to patients. Due to their invasive nature, IMDs are considered to be high-risk devices that require extensive preclinical research and testing. Current early development phases and their associated requirements are reviewed.

**I** mplantable medical devices (IMDs) have been used globally for decades in established and unique clinical settings to restore anatomical and physical functions, improve quality of life, and save human lives. More recently they are achieving prevention, monitoring, and diagnostic functions and are replacing or complementing pharmaceutical therapies. The development of medical devices for commercial use is a complex process that involves considerable time and expense. This article will provide an overview of IMD product development through preclinical testing for the purpose of regulatory approval and commercialisation.

IMDs are introduced into the human body either surgically under direct visualisation and/or through minimally invasive medical interventions using external visual control. Many of these technologies are referred to as



“revolutionary” or “breakthrough” inventions or novel applications of existing technologies. In some cases, they are also considered to be “disruptive” to currently accepted treatments or standards of care and may require the qualification of new medical subspecialties.

With the introduction of new materials, processes, techniques or system designs some marketed IMDs have substantially changed and can also require new regulatory approvals. Transcatheter heart valve implantation using transfemoral or transapical heart access is a recent



example of a disruptive/breakthrough therapy where the redesign of existing surgical biological heart valves and catheter delivery systems enabled the less invasive introduction and implantation of an artificial heart valve into the beating heart without opening the chest, using a heart-lung machine, or suture fixation of the device.<sup>1</sup>

### Medical device regulation

To optimise device evaluation, testing results, and their presentation in a regulatory submission it is essential to understand product development phases and processes, the appropriate international standards guidelines to follow, as well as the regional regulatory requirements.

Bringing new IMDs to patients and commercial markets is governed by country laws, and regional regulations such as the European Union Medical Device Regulation 2017/745 (EU MDR) and the Federal Food, Drug, and Cosmetic Act that is administered by the Center for Devices and Radiological Health (CDRH) of the United States Food and Drug Administration (US FDA). The main purpose of medical device regulation is to evaluate their safety, effectiveness, quality and reliability for target patients. International standards evaluating these areas of interest have been developed by the International Organization for Standards (ISO). The standards are voluntary but can be required in some countries' medical device regulations. There are several ISO standards that are specific to medical devices and provide guidance to manufacturers and regulators in areas such as quality management systems including product design & development (ISO 13485:2016), application of risk management to medical devices (ISO 14971:2019), and clinical investigations of medical devices in human subjects (ISO 14155:2020). As part of the transition to the EU MDR, old "MEDDEV" guidance documents are being replaced. New documents are endorsed by the Medical Device Coordination Group (MDCG) in accordance with Article 105 of the EU MDR. These guidance documents are available on the European Commission Public Health Medical Devices Section website and address many aspects of medical device regulation.<sup>2</sup>

In the past, IMDs were able to be studied and introduced in the European Union noticeably sooner than in the United States. The EU MDR has modified many regulation articles that can

lengthen the submission process. The US FDA has, however, recently initiated a new Breakthrough Devices Program and Guidance document (December 2018) to expedite the market availability of novel medical devices but retains the statutory premarket approval standards. This programme offers manufacturers access to FDA experts to ascertain how to study the device and which regulatory path to use. A Breakthrough Designation request can be sent to the FDA any time before sending a marketing submission.<sup>3,4</sup>

### Medical device classification

The regulatory approval process classifies medical devices according to the type of bodily contact, the duration of contact with the human body and their associated biological effects or risks into Class I (low risk); Class II (moderate risk) (in EU Class IIa – short term use; Class IIb – long-term use) or Class III (high risk) devices. The risk classification of the device will determine its path to market. In the EU, prior to classifying a device, documented statements must be developed that are required for the Technical Documentation file. The EU MDR, Annex II, 1.1, indicates the specific elements of device description and specification along with other product features that can assist in deciding on which risk classification the device will receive.

IMDs in direct contact with tissue, bone, or blood are defined as being high risk, Class III devices and require extensive preclinical testing and clinical trials in the EU and US. In the EU, medical devices can be commercialized after receiving CE marking. (See EU MDR 2017/745 Annex VIII for definitions, rules, on the classification of medical devices, and MDCG 2021-24, October 2021 Guidance on classification of medical devices.) In the United States, market authorisation is granted for Class III medical devices following Premarket Approval (PMA), for Class II devices with a Premarket Notification 510(k) clearance, for some low to moderate risk devices with a De Novo classification, defined as those

devices for which there is no legally marketed predicate device or with a Human Device Exemption (HDE) for patients with rare diseases or conditions. To learn more about FDA Medical Device Classification a web-based tutorial is available on CDRH Learn. (How is My Medical Device Classified? CDR Kimberly Piermatteo, MHA).<sup>5</sup> Table 1 shows device risk classifications with definitions, examples, and the requirements for market authorisation in the European Union and the United States.

### Medical device development phases

Medical product development can be divided into 5 phases:

1. Ideation/discovery;
2. Preclinical research including design specification, prototyping, bench performance testing and *in vitro* and *in vivo* testing;
3. Human clinical trials;
4. Regulatory preparation, review and submission; and
5. Post-market surveillance. Each of these phases will have different timelines depending on the product risk classification and extent and depth of preclinical testing and clinical trials results.

The team should include representatives from engineering research and product development, animal testing, medical/clinical affairs, medical writers, quality, safety, regulatory, manufacturing, packaging, labelling, product management, and marketing.

### New product development team

To reduce communication barriers between device manufacturer departments and improve regulatory submission processes, a project-specified new product development team should be created incorporating members from various stakeholder departments. The team should include representatives from engineering research and product development, animal testing, medical/clinical affairs, medical writers, quality, safety, regulatory, manufacturing, packaging, labelling, product management, and marketing. A diverse interdisciplinary team will provide a wide range of knowledge and experience that can

expedite discussions within and between departments, offer suggestions and generate questions on new findings. Team leaders are traditionally chosen from the engineering and product development group who are responsible

**Table 1. Medical device classification and requirements for market authorisation in the EU and US**

System	Class	Risk	Definition / Examples	Market Authorisation Requirements	
EU	<b>I Basic</b>	Low	Non-invasive devices that do not interact with the human body, non-sterile. no measuring function / Wheelchair, plaster, hospital bed, bedpan, compression stockings	No, self-documentation with CE mark and identification code (UDI)	
	Sub-categories	<b>I<sub>s</sub></b>	Low	Sterile market placement / Personal protection kits	Partial, CE marking
		<b>I<sub>m</sub></b>	Low	Devices with a measuring function / Stethoscope, thermometer, weight scale	Partial, CE marking
		<b>I<sub>r</sub></b>	Low	New subclass for reprocessed or reused products / Surgical instruments, endoscopes	Partial, CE marking
		<b>II<sub>a</sub></b>	Moderate	Inserted in the body short term (60 minutes to 30 days) / Hearing aid, ultrasonic diagnostic device, indwelling catheters, cannulas, tracheal tube	Yes, CE marking
		<b>II<sub>b</sub></b>	Moderate to high	More complex than II <sub>a</sub> devices, inserted or implanted > 30 days / Infusion pump, intensive care monitoring equipment	Yes, CE marking
		<b>III</b>	High	In direct contact with central circulation, nervous system or contains a medicinal product / Pacemaker, prosthetic heart valve, cardiovascular catheters e.g. angioplasty catheters, stent delivery catheters, neurovascular coils	Yes, CE marking
USA	<b>I</b>	Low	Present minimal potential for harm / Manual stethoscope, adhesive bandages, crutches, tongue depressors	510(k) exempt, 510(k)	
	<b>II</b>	Moderate	Higher risk than class I devices / Syringes pregnancy test kits, platelet rich plasma separation kits, electric wheelchair	Premarket Notification 510(k) or De Novo, with or without Breakthrough Designation	
	<b>III</b>	High	Sustain or support life, are implanted, or present potential unreasonable risk of illness or injury / Intraocular lens, artificial heart valves, pacemakers, implanted prosthetics	Pre Market Approval or Human Device Exemption with or without Breakthrough Designation	

for managing information within the team and to company leadership. One should however consider the rotation of team leaders or identify team co-leaders with members who have expertise in the actual development phase. This can improve focus on the relevant goals and timelines in that phase and better address issues or areas of concern. For example, when it is time to develop clinical trial protocols and prepare for human clinical trials, a medical/clinical affairs member of the team would be in a better position to interface with and direct the team rather than someone from the engineering group. Team leader rotation supports growth in member expertise, encourages creativity, and helps

develop new leadership skills and motivates team member involvement.<sup>6</sup>

### New product discovery

Ideas for new medical devices usually arise from the need to treat or alleviate unmet clinical challenges of diseases in a larger patient population. Often clinicians who have considerable knowledge and experience with a specific disease entity will develop ideas to improve patient outcomes. Their patient observations and early research are key for successful collaborations with the medical device industry to participate in early evaluations and define medical device engineers' initial device

concepts, designs, and materials. In the discovery phase, consideration has to be given to anatomical structures, biological reactions, clinical complications, engineering issues, material availability and mechanical limitations. Medical device engineers may have to be knowledgeable in a variety of fields that may include biocompatibility, structural design, electromechanical systems, delivery systems, power management and wireless communication. A complete review of the relevant scientific and medical literature including *in vitro* and *in vivo* animal research and human trial experiences and will be of significant help in understanding the underlying disease process,



current standards of care, device inputs and designs, compatible materials as well as clinical results of similar marketed devices and should be available for submission.

Devices implanted surgically may need new instruments or implant accessories whereas minimally invasive techniques will require additional instruments or delivery devices to bring them to the correct target organ or anatomical location. Changes in visualisation techniques for successful implantation can also be necessary. For example, in transcatheter therapies for structural heart disease the evolution of multimodality imaging such as real-time 3-dimensional echocardiography, computer tomography angiography and 4-dimensional technologies now enables more reliable pre-procedure planning, accurate procedural placement and post-procedural follow-up of these devices.<sup>7,8</sup> Adjunct devices will also need

**Devices implanted surgically may need new instruments or implant accessories whereas minimally invasive techniques will require additional instruments or delivery devices to bring them to the correct target organ or anatomical location.**

development or modification documentation and testing, and regulatory approvals. These documents must also be included in the regulatory submission of the implantable device and may require separate approvals.

### Design control

Design control is an integral part of product development to ensure that the medical device being developed is safe. The intent of design control is to avoid undocumented changes, improve predictability and reduce unanticipated surprises during product development and production. The FDA first included design control requirements in their medical device approval processes and the current version is found in the FDA 21 CFR (Code of Federal Regulations) Part 820.30. In the EU MDR, design control is incorporated in the manufacturer's quality management system addressed in Annex I, Chapters 1 and 2. ISO 13485:2016 includes

design control in section 7.3 and FDA regulation 820.30 is in full alignment with this ISO.

Several distinct phases are incorporated into the design control framework:

1. Design planning with the designation of user and patient needs,
2. Design input,
3. Design output,
4. Design verification, and
5. Design validation. A design history file is required to maintain all documentation of records and show that the device design was developed in accordance with the approved design plan and requirements.

In phase 1, the user needs to identify the intended use of the product, indications for use and the patient population. The intended use is the purpose of the device, the indications describe the disease state or the disorders that the device will diagnose, prevent, alleviate, or cure. Design inputs are design features that are measurable and include all physical, functional, safety and performance requirements of the device. Inputs can be driven by guidance documents, predicate devices, competitive products, industry standards or risk analysis. Design inputs descriptions must be clear and

concise and are tested to “pass/fail” criteria.

Design outputs show that the design input features have been implemented and can be used as guidance documents for device production and assembly. Examples of these documents include device and component specifications, manufacturing procedures and assembly instructions, engineering drawings, and engineering/research logbooks.

Design verification demonstrates that the product was made correctly and consistently meets the design input requirements. Test reports must be documented with objective evidence in the design history file and confirm that the design output meets the design input. Design validation ensures that the correct product was consistently manufactured and meets all the identified user needs and intended uses.

### Preclinical research and testing

Device prototyping is necessary to identify the optimal design, compatible materials and processes of device manufacture. Most early prototypes are produced by hand, may go through several iterations and not always be constructed from final production materials. Physical simulations using non-clinical bench performance tests are conducted to validate the plausibility of the device concept under anatomical and physiological conditions. These tests can cover mechanical and engineering performance evaluations such as fatigue testing, material wear, tensile strength, compression, and burst pressure. Tests are performed using *ex vivo*, *in vitro*, *in situ* animal or human tissue, animal carcass, or human cadavers. All testing is to be governed by documented protocols. Regulatory submissions require complete test reports including all tests performed, test objectives and methods, pre-defined pass/fail criteria, results summaries, discussions, and conclusions. A table of test summaries is also often requested by regulatory bodies. The overall objective is to demonstrate substantial equivalence of the new IMD to a predicate device or reasonable assurance of safety and effectiveness of the IMD and that it can be durable and consistently produced for human use *before* implanting it in a human.

In the early design phase, bench testing can pinpoint potential design and mechanical flaws and check on the performance and safety of the device. After the initial design has been finalised, bench testing will document that the device is

meeting the design specifications. When pre-production prototypes or production units are available, they will also be tested to show appropriate safety and performance. Technical testing of materials and electronic components is also included in the proof of concept testing. Testing strategies for bench testing should be carefully reviewed by the product development team to make sure all required and appropriate tests are transparent and complete. This includes test results for pre- and post-marketing requirements such as comparative testing with earlier models, with other similar marketed models or for marketing brochures and labelling.

Following bench and technical testing, the materials and/or IMD must undergo further biological evaluations and biocompatibility testing to demonstrate that it will perform its intended function without causing any short-term or long-term adverse effects to the human body such as cytotoxicity, mutagenicity and genotoxicity, haemocompatibility irritation, sensitization, acute systemic toxicity, subacute chronic toxicity, carcinogenicity, or material-mediated pyrogenicity. *In vitro* and *in vivo* animal testing are often performed to evaluate the interaction between the IMD and body fluids, cells or tissue of the recipient. The animal models chosen for IMD testing will be dependent on the device materials and IMD implantation location. The FDA has also recently released guidance documents that are focusing on improved efficiency of medical device testing and the implementation of well-designed large animal studies to be used to leverage safety tests such as systemic toxicity, chronic implantation and *in vivo* thrombogenicity and thereby replace the traditional small animal model.<sup>9</sup> The ISO 10993 – *Biological evaluation of medical devices* consists of a series of 20 guidance documents that can help the manufacturer select the most appropriate tests to screen for device biocompatibility to manage biological risk. Part 1 of ISO 10993 defines and describes the applicability of the additional 19 parts and the necessity to evaluate results within a risk management process. Attachments A through F of ISO 10993-1 provide very relevant recommendations, examples and summaries of reports to be written for the biocompatibility

section of the regulatory submission.

A final important element of the early design phase is the creation of a risk management plan and assignment of a team that is knowledgeable about the construction, function, production and use of the medical device and risk management tasks. Risk management is now mandated by EU MDR in Article 10(2) and is described in Section 3 of Annex I. The US FDA 21 CFR 820 also addresses risk management in their Quality Systems regulations. Both use the ISO 14791:2019 *Medical Devices – Application of risk management to medical devices* as their guidance document. The purpose of risk management is to make sure that the medical device is safe which is defined as having a product that is free from unacceptable risk.

The purpose of risk management is to make sure that the medical device is safe which is defined as having a product that is free from unacceptable risk.

The risk management process is active throughout the product life cycle of all medical devices from product design and development to final market withdrawal. Most medical device manufacturers have been managing risk with a Failure Modes and Effects Analysis (FMEA) (IEC 60812:2006) that has traditionally been managed by device engineering groups. Design FMEAs however specifically look at component failures and their consequences and identify how to mitigate the failure risk. This is only part of the overall risk management process. Risk management as per ISO 14971 focuses on the identification and analysis of known and foreseeable product hazards and resulting human harms, followed by a calculated estimation of the acceptability of the risk. Thereafter risk control options, risk control measures, and residual risk are identified and verified. This analysis is best documented in a dynamic hazards matrix that requires regular review and updates especially when new information is available such as production data, complaint information, post-market surveillance, medical literature and clinical evaluation report updates. A risk management file must also be established that contains relevant records and documents from the ongoing risk management process that can be submitted with a regulatory submission or presented to a regulatory auditor.

Developing new and innovative IMDs is an exciting but challenging and often resource-intensive endeavour. To keep new products in the pipeline a company has to commit to a culture



where innovative ideas are nurtured and quickly initiated and where the company infrastructure is committed to the development and pre-clinical phases knowing that risks of failure may be high. Despite the recent increase in regulatory hurdles, for a complete and successful IMD submission, the early preclinical phases of IMD development require thorough planning, attention to detail, appropriate and rigorous testing protocols and accurate and complete documentation.

**Disclosures and conflicts of interest**

The author declares no conflicts of interest.

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# EU sourcing requirements for animal-derived materials

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## Abstract

Regenerative medical products derived from animal tissue have been used to successfully treat millions of patients. As they are manufactured from animal sources, there are bio-contamination and biocompatibility risks that must be addressed in accordance with ISO 22442 for receipt of the CE Mark and subsequent EU commercialisation. This article discusses important regulatory animal sourcing requirements associated with medical devices that cover these biological risks. These requirements include risk management, animal health controls, quality system elements, and demonstration of safety related to potential transmissible pathogens. The necessary information needs to be presented in the form of reports, risk analyses, and other documentation.

**R**egenerative medicine is a complex, interdisciplinary field that utilises bioactive substances, cells, and biomaterials with the goal of repairing and restoring bodily tissues and organs of humans. An area of extensive research and development of regenerative implants involves the use of animal-derived tissues as a standalone regenerative construct or as a delivery platform for biological agents. Clinically, regenerative applications of animal-derived tissues have widespread use in wound care, orthopaedics, dentistry, cardiology, general surgery, urogynaecology, neurology, and other medical fields. Some commonly known animal-derived products include advanced wound dressings, synthetic bone grafting materials, dural substitutes, and biological heart valves.

The fundamental scientific reason why animal-derived tissues are ideal implantable materials is that there is extensive homology

between animal extracellular matrices and human analogues. This relationship is mainly due to collagen and other macromolecules such as elastin, hyaluronic acid, and sulphated glycosaminoglycans, which are the principal components of all extracellular matrices across species and are remarkably similar in their structures among mammals. Given this extensive similarity of extracellular matrix molecules, the main concern for implantation of

animal tissues relates to the human antigenic response against animal cells and nucleic acids that reside within the tissue. Accordingly, an entire field has emerged that involves the engineering and manufacturing of extracellular matrices and collagen that remove the unwanted animal cellular and nucleic acid components, with the goal of leaving the extracellular matrix intact. In this regard, animal-derived, decellularised extracellular matrix tissues



*Porcine heart valves*

become almost “humanised” in their resemblance to human counterparts.

Given their abundance, relative low cost, and controls due to governmental and industrial regulations, tissues from swine (porcine) and cattle (bovine) are by far the most utilised in commercially approved animal-derived medical products, both in Europe and elsewhere. No matter the animal source, however, compliance with several important standards must be demonstrated for receipt of the CE Mark for a medical device. Of these standards, the animal tissue sourcing requirements of the ISO 22442 series<sup>1-4</sup> are the most relevant and will be discussed in this article.



### ISO 22442-1 application of risk management

Risk management requirements are detailed in ISO 22442-1,<sup>1</sup> which primarily relate to the risks of product bio-contamination and bio-incompatibility due to the use of animal-derived tissues. The device manufacturer needs to provide a risk analysis that considers the following possible product hazards:

1. Parasites and unclassified pathogenic entities,
2. Bacteria, moulds, and yeasts,
3. Viruses,
4. Transmissible spongiform encephalopathy (TSE) agents, and
5. Pyrogenic, immunological, and toxicological reactions.

Another important aspect related to ISO 22442-1 compliance is a justification for why animal tissues are required *in lieu* of synthetic alternative materials, materials from less risky animal species, or from human origin. Typically, a justification involves a scientific and clinical review of the relevant literature and an overall assessment of the product risk to benefit ratio. Finally, ISO 22442-1 requires surveillance of animal zoonosis to provide on-going re-assessment of the risk analyses. As an example, porcine derived materials are inherently less risky than their equivalent bovine materials, since a TSE agent, bovine spongiform encephalopathy (BSE), has been found in bovines, but to date, porcine animals have not been found to be infected with a TSE agent.

Accordingly, a manufacturer of porcine derived materials used in their medical device must continuously monitor the scientific literature for evidence of a possible porcine spongiform encephalopathy agent (PSE), which of course, if ever found, could greatly impact the risk profile of their medical device.

### ISO 22442-2 controls on sourcing, collection and handling

ISO 22442-2<sup>2</sup> provides the necessary controls for animal-derived tissues and substances, at

Risk management requirements are detailed in ISO 22442-1, which primarily relate to the risks of product bio-contamination and bio-incompatibility due to the use of animal-derived tissues

collection and handling of tissue, storage, transportation, labelling requirements, and auditing responsibilities.

### ISO 22442-3 and ISO 22442-4 validation and principles concerning the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents

As sterile medical devices must meet a sterility assurance level (SAL) of  $10^{-6}$ , there is a similar concept that must be demonstrated to establish viral safety for devices derived from animal sources. A manufacturer must establish that the manufacturing process inactivates or eliminates potential viral contaminants to a level that renders the animal tissue-based device a low viral risk. This level is quantified as a log reduction value (LRV) via a viral clearance

study. Typically, the process begins with a formal literature review with a protocol, whose requirements are stipulated by ISO 22442-3.<sup>3</sup> Viruses that are relevant for the specific zoonosis situation, based on tissue source, are identified through the review. This enables the manufacturer to identify specific viral risks and determine the approach required in the manufacturing process to eliminate any identified zoonotic viruses. In addition, this information is utilised in the selection of a virus panel used for upcoming viral inactivation studies.

A manufacturer must establish that the manufacturing process inactivates or eliminates potential viral contaminants to a level that renders the animal tissue-based device a low viral risk.



Another important aspect of the literature review is the determination of which manufacturing steps may inactivate and/or eliminate viruses, and what theoretical viral reduction levels may be obtained by these processes according to the literature. Sterilisation usually plays a key role in viral inactivation as well; for example, radiation and chemical sterilisation methods usually offer significant viral inactivation capabilities. In this planning phase, key considerations for the inactivation of viruses are also evaluated, including the effects of the tissue substrate and preceding manufacturing steps on viral inactivation efficiency. Finally, the literature review identifies the key processing parameters that affect viral inactivation, which are essential for establishing critical process controls that must be maintained for eventual viral inactivation validation.

In most cases, a medical device manufacturer will proceed with a viral inactivation study that evaluates the efficacy of the selected manufacturing steps to inactivate and/or

eliminate viruses, with the goal of generating LRV data. However, in some circumstances, a manufacturer may rely upon the literature and a risk-based approach *in lieu* of performing a prospective viral inactivation study. This may occur when literature studies are so highly relevant that they closely match a viral inactivation step of the manufacturing process, and the generated log reduction values from the literature studies are directly applicable. Manufacturers may also proceed with a hybrid approach that is both literature-based and utilises viral inactivation studies.

The design and execution of viral elimination/inactivation studies must be performed in accordance with the requirements ISO 22442-3. Elimination is a process where viruses remain intact but are removed from the tissue substrate whereas inactivation is causing the alteration of the virus by the manufacturing process that renders a virus non-infectious. Prior to executing formal elimination/inactivation studies, a protocol should be written that documents the following:

1. Risks identified per ISO 22442-1,
2. Anticipated zoonotic viral agents,
3. A relevant virus panel that usually includes four virus types: RNA and DNA viruses, both enveloped and non-enveloped,
4. Identification of the manufacturing processes selected to eliminate/inactivate viruses,
5. Demonstration of the validity of a scaled down process used in a viral testing laboratory in comparison with the actual full-scale production process, and
6. Methods for the calculation of viral reduction factors and the method for the estimation of reduction kinetics, when applicable.

Viral elimination/inactivation studies are then conducted in accordance with the protocol, and log reduction values for each evaluated manufacturing step are obtained.

The last requirement of the ISO 22442-3 process is the writing of a final report that includes the literature review and information obtained from executed viral elimination/



inactivation studies. The efficacy of the overall manufacturing process to reduce the four virus types (RNA, DNA; enveloped and non-enveloped viruses) is provided. Finally, the report identifies critical manufacturing parameters with limits that need to be maintained during the production process for assurance of viral inactivation.

For animal sources that represent a TSE risk, such as cattle, ISO 22442-4<sup>4</sup> provides analogous information to the viral inactivation requirements provided in ISO 22442-3 for TSE inactivation. However, TSE inactivation studies for tissue and collagen materials are rarely performed, since the proven methods required to inactivate the TSE agent, i.e., abnormal prion protein, are impractical to use in creating a medical device. These treatments include incineration, chlorination, and strong alkali in combination with substantial heat, all of which effectively destroy tissue and collagen preparations. Therefore, when TSE inactivation studies are unable to be performed, the risk of potential TSE contamination is mitigated by an alternative risk management strategy per ISO 22442-1, which usually depends on sourcing controls. Generally, almost all tissue and collagen preparations are derived from connective tissue, which are known as a low TSE infectivity risk. Combined with strong governmental agricultural controls, usually the risk management strategy of sourcing control is accepted by regulatory bodies as a means of demonstrating an acceptable risk with respect to TSE transmission.

### Special current zoonotic concerns

As discussed previously, zoonosis monitoring is an important requirement of ISO 22442-1 to understand if the risk profile associated with animal tissue sourcing has changed. Current major zoonosis concerns are related to the SARS-CoV-2 coronavirus (cause of COVID-19 pandemic) and in the case of porcine-derived materials, African swine fever virus.

Given the concern related to the SARS-CoV-2 coronavirus, manufacturers have incorporated this transmissible agent into their surveillance. Fortunately, commercial swine and cattle livestock have not been shown to be

**Current major zoonosis concerns are related to the SARS-CoV-2 coronavirus (cause of COVID-19 pandemic) and in the case of porcine derived materials, African swine fever virus.**

infected with this virus. Even in the event of a livestock infection, it is likely that most tissue and collagen manufacturers will determine that their existing methods are highly effective for inactivation of SARS-CoV-2 coronavirus. This is because coronaviruses are RNA enveloped and are highly susceptible to typical processes used in collagen manufacturing, which include alcohol and alkaline treatments, radiation sterilisation, and other physicochemical methods.

African swine fever is a deadly disease of pigs that has seen widespread outbreaks across Africa, Asia, and Europe since 2007. Fortunately, the causative African swine fever virus is a threat to swine but has no impact on human health. Accordingly, the main concern for manufacturers is a supply chain issue where tissue raw materials may become limited. The animal controls instituted by governmental agencies have prevented any significant contamination of commercial swine livestock in most geographic markets, but vigilance and monitoring need to be maintained for this swine disease.

In summary, the use of tissue and collagen materials derived from animal sources are commonly used in many regenerative medical devices that have been successfully used to treat millions of patients. To protect patients from bio-contamination and bio-incompatibility risks, device manufacturers must adhere to the animal tissue sourcing requirements of ISO 22442. Compliance with these standards will ensure that animal-derived medical devices remain safe for patients.

### Acknowledgements

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### Disclosures and conflicts of interest

The author declares no conflicts of interest.

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# The clinical development plan

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## Abstract

The Medical Device Regulation (MDR) mentions the term “Clinical Development Plan” (CDP) only twice, both of which are in Annex XIV. This article aims to delve deeper than the MDR into what the CDP entails and to propose the best strategies for a manufacturer to plan their medical device’s clinical evaluation.

Although there is no official definition of the CDP, one may simply refer to it as an overview of all the clinical investigations that have either been performed, are ongoing, or are planned in the near future, presented in the Clinical Evaluation Plan (CEP) of the medical device under evaluation.

This article is intended to assist medical device manufacturers and medical writers to leverage the CDP as a tool to showcase their clinical evaluation strategy and plan.

## The Clinical Development Plan (CDP) as per the Medical Device Regulation (MDR)

The MDR provides a complete list of criteria to continuously conduct and document a clinical evaluation in Annex XIV,<sup>1</sup> where we get introduced to the term CDP for the first time as follows:

*“To plan, continuously conduct and document a clinical evaluation, manufacturers shall establish and update a clinical evaluation plan, which should include (amongst other criteria):*

- a **clinical development plan** indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF [Post-Market Clinical Follow-up] as referred to in Part B of this Annex with an indication of milestones and a description of potential acceptance criteria.



- generate, through properly designed clinical investigations in accordance with the **clinical development plan**, any new or additional clinical data necessary to address outstanding issues.”

## The relationship between CDP and CEP

The CEP outlines the clinical strategy that the manufacturer shall follow to justify the safety and performance of their device in accordance with the General Safety and Performance Requirements (GSPR) of the MDR. The CDP is a subset of the CEP focusing specifically on the clinical investigations for the given device that:

- a. Have already been conducted, preferably with a full clinical investigation report available
- b. Are being conducted with a full clinical investigation protocol available, or
- c. Are planned in the future – these could include pilot, pivotal, or PMCF studies. Preferably, the synopsis of this study should be included in the CDP in this case.

## How to present the CDP in the CEP

Annex I of ISO 14155:2020 explains, in detail, the differences between pilot, pivotal, and PMCF clinical investigations and acts as an excellent reference for the CDP. (See the September 2021 issue of MEW for a flowchart of ISO 14155:2020, p. 96) .

As for the presentation itself, the CDP may be written in paragraphs or presented as a table. Questions to ask during the formulation of a CDP may include:

1. Based on the literature review results and the CE mark status of the device (i.e. pre-CE

mark or already CE marked), what kind of clinical investigation (CI) are we looking at for the evaluated device? Is it a pilot/pivotal or post market clinical follow-up (PMCF) CI?

2. Has the possibility to do a statistically sound, non-randomized CI, instead of a randomised one, been explored? (Randomized studies are not always essential for regulatory approval of medical devices depending on the specific case, type and class of device. It should however be ISO 14155:2020 compliant irrespective of study design).
3. Have we outlined the inclusion/exclusion criteria in the CDP of our CIs?
4. What were the endpoints/acceptance criteria of our previous clinical investigations? Has it been clearly presented in the CDP? Based on the results of that study, do we want to test something new or gather more robust information on safety? In which case, the study design for the upcoming CI may include these new parameters as the primary and/or secondary endpoints.
5. Is this study design in line with our regulatory strategy and business plan for market access?
6. Might we gain a high-quality publication out of this CI?
7. Do we plan to perform “off-label use” clinical investigations to expand the indications of the evaluated medical device? If so, then this may be included as part of the CDP as well.

## MDCG document references for the CDP writing

A. The Medical Devices Coordination Group (MDCG) Document – MDCG 2020-13 – *Clinical evaluation assessment report template* – helps outline what the notified bodies are looking for whilst reviewing the Clinical Evaluation documentation. Regarding the CDP/Strategy, the document states that the notified body should ensure that the CDP is outlined as per Part B of MDR Annex XIV. Interestingly, the document outlines that “A detailed description of the clinical development plan is not required for the purpose of this template unless there are specific concerns”, which may be interpreted that the notified bodies are not obliged to scrutinise the nitty-gritty details of the CDP at this stage of review unless something is inherently questionable in the clinical development strategy. Hence, one may assume that a well-presented CDP in the CEP is sufficient for the notified body review.

The document also states, notably with regards to the clinical development strategy:

“Section K: The voluntary clinical consultation on the clinical development strategy (Article 61(2))

1. Expert Panel consultation reference
2. Expert Panel recommendations:
  - Have the views of the Expert Panel been given due consideration by the manufacturer?
  - Has this been included in the clinical evaluation report?
  - Is there any divergence between the manufacturers’ clinical development strategy and the views of the expert panel? If yes – what is the justification for this?
  - Is this acceptable? Explain why.

B. Another MDCG guidance document titled *The MDCG Guidance on Clinical Evaluation (MDR)/Performance Evaluation (IVDR) of Medical Device Software (MDSW)*, published in March 2020, also mentions the CDP twice. The first reference is to quote Annex XIV of the MDR, and the second mention is regarding the continuous update of the clinical evaluation, which mentions the following:

“The safety, effectiveness, and performance of the MDSW should be actively and continuously monitored by the manufacturer.

Such data may include, but is not limited to, post-market information such as complaints, PMCF/PMPF data, real-world performance data, direct end-user feedback or newly published research / guidelines and should be subject to the clinical evaluation (MDR) / performance evaluation

(IVDR) principles. The unique level of connectivity of MDSW facilitates access to Real-World Performance data, which can be used for multiple purposes, including, but not limited to:

- timely detection and correction of malfunctions;
- detection of systematic misuse;
- understanding user interactions;
- conducting ongoing monitoring of clinical performance;
- improving effectiveness;
- developing the claims in the clinical development plan (MDR) or future releases”.

Although the above MDCG guidance document is meant for medical device software, it focuses our attention on how the real-world data may be leveraged to develop the claims in the CDP. This is an important consideration as performance and safety claims are seldom well thought out at the clinical evaluation stage by some manufacturers. By using the data gathered from the clinical investigations as well as during post-marketing surveillance (PMS), the manufacturer may revisit the safety and performance claims and take these considerations for their CDP and designing of upcoming clinical investigations.

## Conclusion

The CDP is an effective tool that could facilitate manufacturers to demonstrate the extent of the clinical evaluation planning for their medical devices. It summarises the clinical investigations that are either planned, ongoing or already performed, based on the risk class and CE mark status of the device. The addition of this section to the CEP helps reinforce and demonstrate the regulatory and clinical strategy where standards such as ISO 14155:2020 and MDCG guidance documents further act as supportive references to ensure appropriate methodology and wording.

The role of a medical writer to create such a

section is of particular importance as they not only foresee the entirety of the clinical evaluation at the very early stages of the clinical evaluation planning but also offer early support to the Regulatory, Marketing, R&D and Clinical departments to harmonise their language and facilitate the overall goal of achieving regulatory approval for the medical device. This unique, in-depth, and bird’s-eye view of a complex clinical evaluation process is a stronghold of the medical writer and should be leveraged by manufacturers to ensure high-quality deliverables.

Overall, through a well-presented CDP, the manufacturer may demonstrate, early on in their clinical evaluation process, the safety and performance claims for their medical device with a strategy on how the clinical evidence shall be gathered to justify these claims. Therefore, despite the sparse mention of the term “Clinical Development Plan” in the MDR, one may appreciate the hidden importance of such a tool to enhance the quality of their technical and regulatory documentation.

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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.

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# A beginner's guide to writing clinical investigation plans and reports for medical devices

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## Abstract

A clinical investigation plan for a medical device must outline and justify all objectives of the clinical investigation, present and justify the investigational design and methodology, and state principal features of the statistical analysis. A clinical investigation report should summarise the plan, explain any deviations from it, and present and discuss the results of the clinical investigation. Preparing clinical investigational documents requires collaboration with numerous professionals with expertise in clinical practice, statistics, data management, monitoring, and regulatory requirements. While separate guidelines apply for medical devices and pharmaceuticals, with differences in terminology and safety reporting among other factors, they offer similar guidance on good clinical practice, adapted for the product type. As a medical writer, you should not be afraid to ask questions when things are unclear, or to offer input.

**D**ue to recently implemented regulations for medical devices and in vitro diagnostics (IVD), the medical device industry is taking a major step towards the strictly regulated world of pharmaceuticals. Clinical data requirements for medical devices and IVD products have been sharpened considerably, and the previously feasible option of riding piggyback on clinical data from similar, marketed products has become very difficult.

Many legacy devices (i.e., existing CE-marked

devices) are therefore in a situation where they need to acquire more clinical data, sometimes complemented by slimming their device claims to limit the amount of data required. Devices not yet on the market need a plan to collect sufficient clinical data before applying for their CE mark. The market for compiling study documentation for the medical device industry is therefore booming. But how do you get started writing clinical investigation plans (CIPs) and reports (CIRs) if you have no previous experience from the medical device industry, or if you have no experience in writing clinical study documents at all?

## Regulations

First, make sure to comply with applicable regulations, standards, and guidelines. In the EU, medical devices are regulated under the Medical Device Regulation (MDR),<sup>1</sup> IVD products under the In Vitro Diagnostics Regulation (IVDR),<sup>2</sup> and pharmaceuticals under the Clinical Trials Regulation (CTR).<sup>3</sup> Medical device investigation protocols must follow the ISO 14155 standard for good clinical practice (GCP)<sup>4</sup> and IVD study protocols the ISO 20916,<sup>5</sup> whereas the pharmaceutical industry follows the International Conference on Harmonization guideline E6 (ICH E6).<sup>6</sup>

Always consider if other standards (e.g., product-specific) and national guidelines also apply. Although the EU is in the process of centralising guidance for collecting clinical data, the work is not complete and additional requirements may exist. In case of differences between standards, the most stringent requirements always apply. This article will focus on medical devices regulated by MDR<sup>1</sup> and ISO 14155.<sup>4</sup>

## Terminology

Although the medical device industry is incorporating increasing vocabulary from the pharmaceutical industry, differences still exist. Some of the most important differences in terminology are presented in Table 1.

Clinical studies are divided into phase I to phase IV studies, whereas clinical investigations use a different terminology referring to pre- and post-market investigations, where pre-market clinical investigations are further divided into pilot stage or pivotal stage investigations.<sup>4</sup>

## Before starting – understand where the clinical investigation puzzle piece will fit

When embarking on writing a CIP, start by reading the clinical evaluation plan (including the clinical development plan), clinical evaluation report, risk management report, and if available, the post-market clinical follow-up (PMCF) plan. If these have not been recently performed or updated, stop, and take a step back. They are essential building blocks laying the foundation for planning a clinical investigation, as described below. Ultimately, results from the completed investigation will be fed back into the PMCF report and into the risk analysis and clinical evaluation documents, which should be updated with the new clinical data, re-assessing their benefit-risk conclusions. This feed-back loop between risk

analysis, clinical evaluation, PMCF, and clinical investigations, is illustrated in Figure 1.

## Clinical evaluation

A clinical evaluation is a requirement for all medical devices according to the MDR. During a clinical evaluation, pertinent data in relation to the device under evaluation and similar devices

A well-performed clinical evaluation identifies the need for a clinical investigation as well as appropriate endpoints, acceptance criteria, and investigational design, and hence lays the basis for planning a clinical investigation.

**Table 1. Differences in terminology between the medical device and pharmaceutical industries**

Medical device industry		Pharmaceuticals
<b>Medical device</b>	<b>IVD medical device</b>	<b>Pharmaceuticals</b>
Clinical investigation	Clinical performance study	Clinical study or clinical trial
Intervention	–	Treatment
Investigational medical device (IMD)	IVD medical device under investigation	Investigational medicinal product (IMP)
Performance or effectiveness	Performance	Efficacy
Investigational design	Clinical performance study design	Clinical study design
Clinical investigation plan (CIP)	Clinical performance study protocol (CPSP)	Clinical study protocol (CSP)
Clinical investigation report (CIR)	Clinical performance study report (CPSR)	Clinical study report (CSR)
Adverse device effect (ADE)	Adverse device effect (ADE)	Adverse drug reaction (ADR)

is identified through a systematic literature review, and by gathering manufacturer data. The state-of-the-art of the medical field is defined and the clinical data is appraised, analysed, and summarised in a clinical evaluation report. Potential gaps between existing data and data required by current regulations, are detected, and highlighted. In other words, a well-performed clinical evaluation identifies the need for a clinical investigation as well as appropriate endpoints, acceptance criteria, and investigational design, and hence lays the basis for planning a clinical investigation.<sup>1,7</sup>

**Risk analysis**

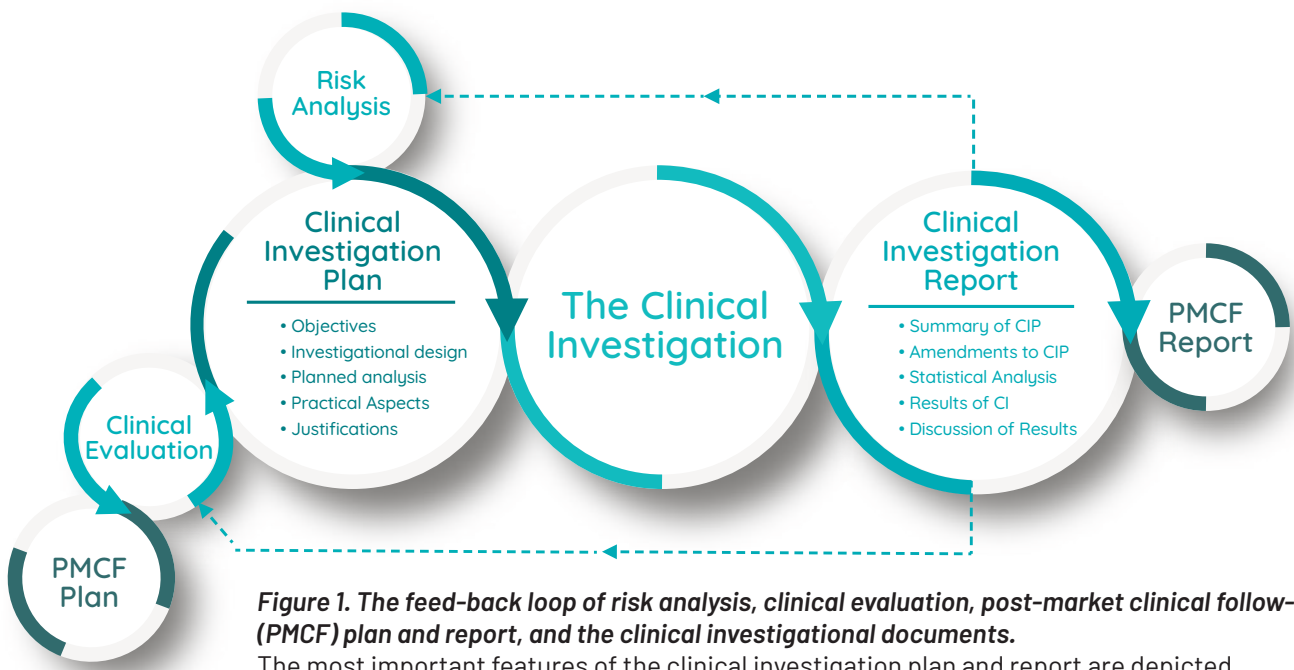
Risks associated with the investigational medical device and any related clinical procedure should also be estimated when planning a clinical investigation, in accordance with ISO 14971.<sup>8</sup> Residual risk according to an initial risk analysis, and risks to the subject related to the clinical procedure or required follow-up procedure, must be balanced against anticipated benefits. In simpler words, a risk-benefit balance must be achieved.<sup>4</sup>

**The clinical investigation plan**

The CIP is the key document of the clinical

investigation, and the basis of the application sent to the Ethics Committee (EC), and potential competent authority, for approval.

A CIP must clearly outline all objectives of the clinical investigation and justify them based on scientific and ethical principles.<sup>4</sup> The CIP should present the investigational design and methodology, including details on intervention and control groups, number of visits, their timepoint and content, defined endpoints, and a rationale for the chosen design. A way to facilitate the understanding and presentation of the investigation is to include a schematic figure of the overall clinical investigational design.



**Figure 1. The feed-back loop of risk analysis, clinical evaluation, post-market clinical follow-up (PMCF) plan and report, and the clinical investigational documents.**

The most important features of the clinical investigation plan and report are depicted.

Abbreviations: CI, clinical investigation; CIP, clinical investigation plan; PMCF, post-market clinical follow-up.

In Figure 2, an example of such an image from a fictional clinical investigation is presented. It is also common, and advisable, to include a table summarising the frequency and timing of clinical visits, and what will be done during each visit (e.g., procedures, lab tests, etc.). This table is called the schedule of events or schedule of activities, and is equivalent to the similar table that would be found in a clinical study protocol for an investigational medicinal product.

Principal features of the statistical analysis to be performed must be included in the CIP, as well as practical aspects such as the organisation, conduct, monitoring and record-keeping of the clinical investigation. For example, processes for how the informed consent shall be obtained, and how to capture data for each enrolled subject, should be specified. Importantly, all anticipated adverse device effects (i.e., adverse events related to the use of an investigational medical device) must be presented, together with a rationale for the related benefit-risk ratio.<sup>4</sup>

The coordinating investigator and the sponsor must sign off on the content of the CIP before the application is submitted. Principal investigators (PIs) for all participating sites, must agree to conduct the investigation accordingly, typically

by signing the final CIP (i.e., the version approved by the EC and competent authority). Any changes to the CIP after its approval, must be described in an amendment that must also be approved, if considered substantial.<sup>4</sup>

**Consider keeping details out of the CIP**

Although all information required by applicable regulations and guidelines should be present in a CIP, it's not always necessary to include a full description of this information, e.g., when it comes to data management, statistics, and monitoring. An option is to provide a short description in the CIP and refer to a separate document for details. This may save time and reduce costs, as these separate documents can be updated without affecting the CIP, thus reducing amendments, and approval rounds. Note however, that for less complex investigations it can be easier to keep everything in the CIP.

**The clinical investigation report**

Once the investigation is closed and the statistical analysis has been performed, it's time to write the CIR. A CIR is always required, even if the clinical investigation is terminated prematurely. The main goals of the CIR are to describe the clinical

investigation's design, conduct, statistical analysis, and results.<sup>4</sup> In other words, the CIR should summarise the CIP, explain any deviations from it, and present and discuss the results of the clinical investigation. The discussion should include a critical appraisal of the results compared to stated objectives.<sup>4</sup>

The CIR must include data from all participating investigational sites so not to exclude any non-favourable data, and must never reveal subject identity. Ideally, all PIs should review the CIR. The final CIR requires signatures from the sponsor and coordinating investigator (or PI for single-centre investigations), before being made available to the EC and/or applicable regulatory authorities, depending on the country.<sup>4</sup> The results from the clinical investigation should also be published in a publicly accessible database, and as mentioned above, should be used to update the risk analysis and clinical evaluation.

**Differences between medical devices and pharmaceuticals**

So, what then are the differences between writing study documentation for pharmaceuticals and medical devices? Well, except for the different guidelines and terminology already mentioned,

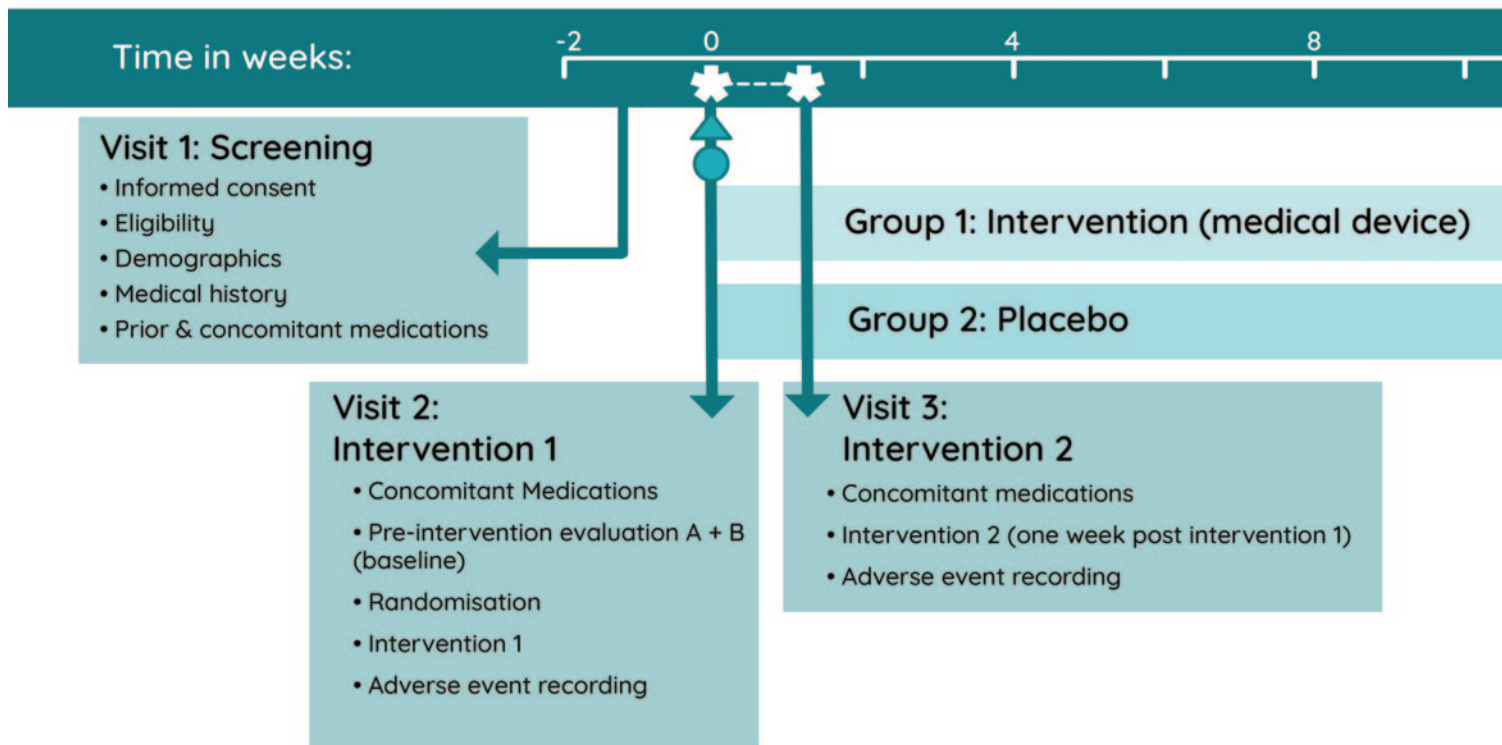


Figure 2. Overall clinical investigational design for a fictional clinical investigation.

**Table 2. Important differences between study/investigational documentation**

	Pharma	Medical devices
GCP guideline/standard:	ICH E6	ISO 14155 (medical device) ISO 20916 (IVD medical device)
Templates on study/investigational documents:	Mainly differences in structure and order of content	
Terminology:	Clinical study/trial, treatment, effect etc.	Clinical investigation, intervention, performance etc.
Safety reporting:	Differences in what to report and reporting timelines	

not that much. While separate guidelines apply, they offer similar guidance on GCP, adapted for each product type. Templates for clinical study/investigational documents provided in the guidelines also have a very similar content, although they have a different structure.

If you are preparing CIP and CIR templates from scratch, you can follow the order of the template offered in ISO 14155. If you already have a template according to ICH E6 (i.e., for a pharmaceutical product) you might use that as a basis, adjusting where needed to comply with regulations and guidelines for medical devices. Other sources for templates may depend on the country where the investigation is conducted,

e.g., the Swiss Association of Research Ethics Committees have published a CIP-template on the SwissEthics website.<sup>9</sup> There is no regulatory requirement to present the content in a certain order, as long as all required information is provided. Table 2 summarises important differences between medical devices and pharmaceuticals to consider when writing study/investigational documents.

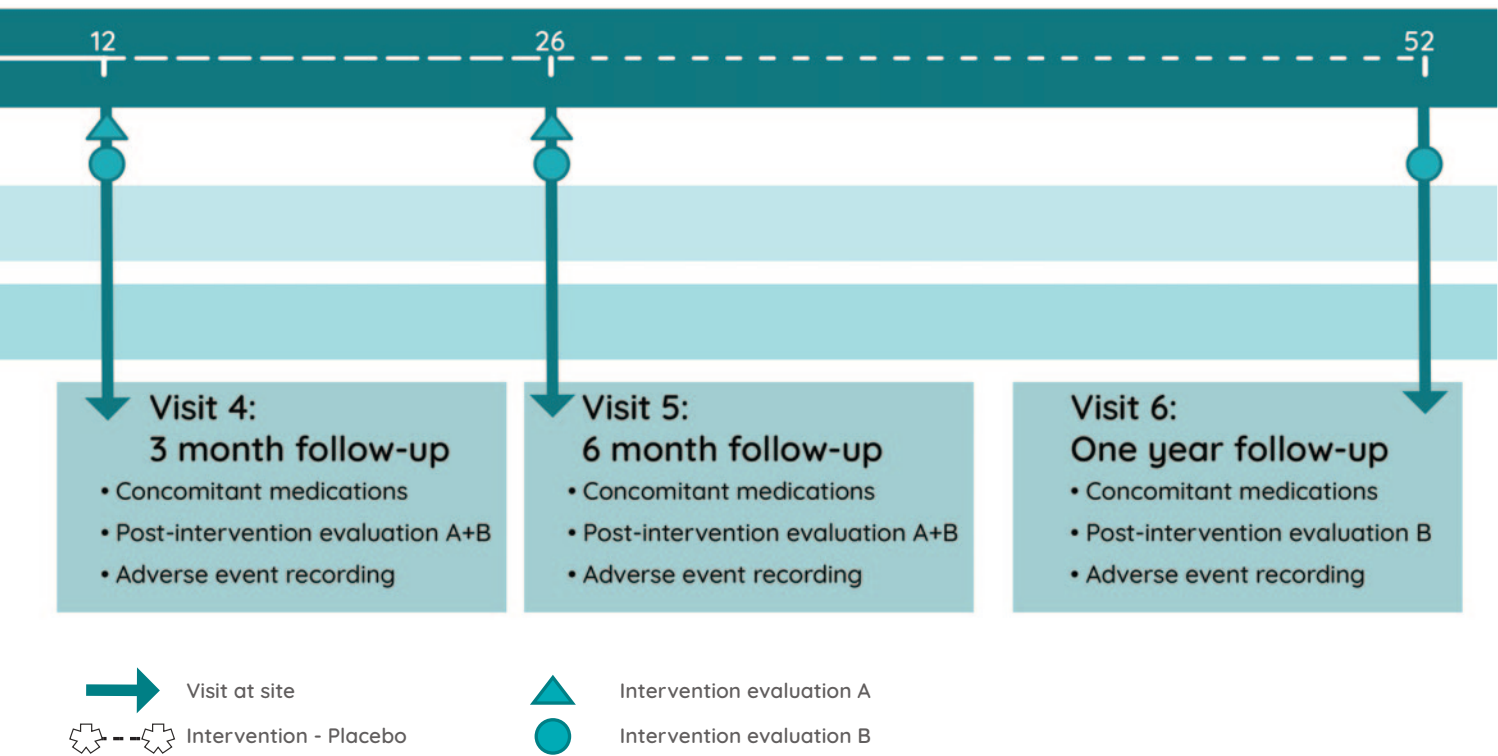
**Risk assessment and reporting**

Risk assessments are generally performed at an earlier stage and are in general more structured for medical devices than for pharmaceuticals, with more procedures around risks including

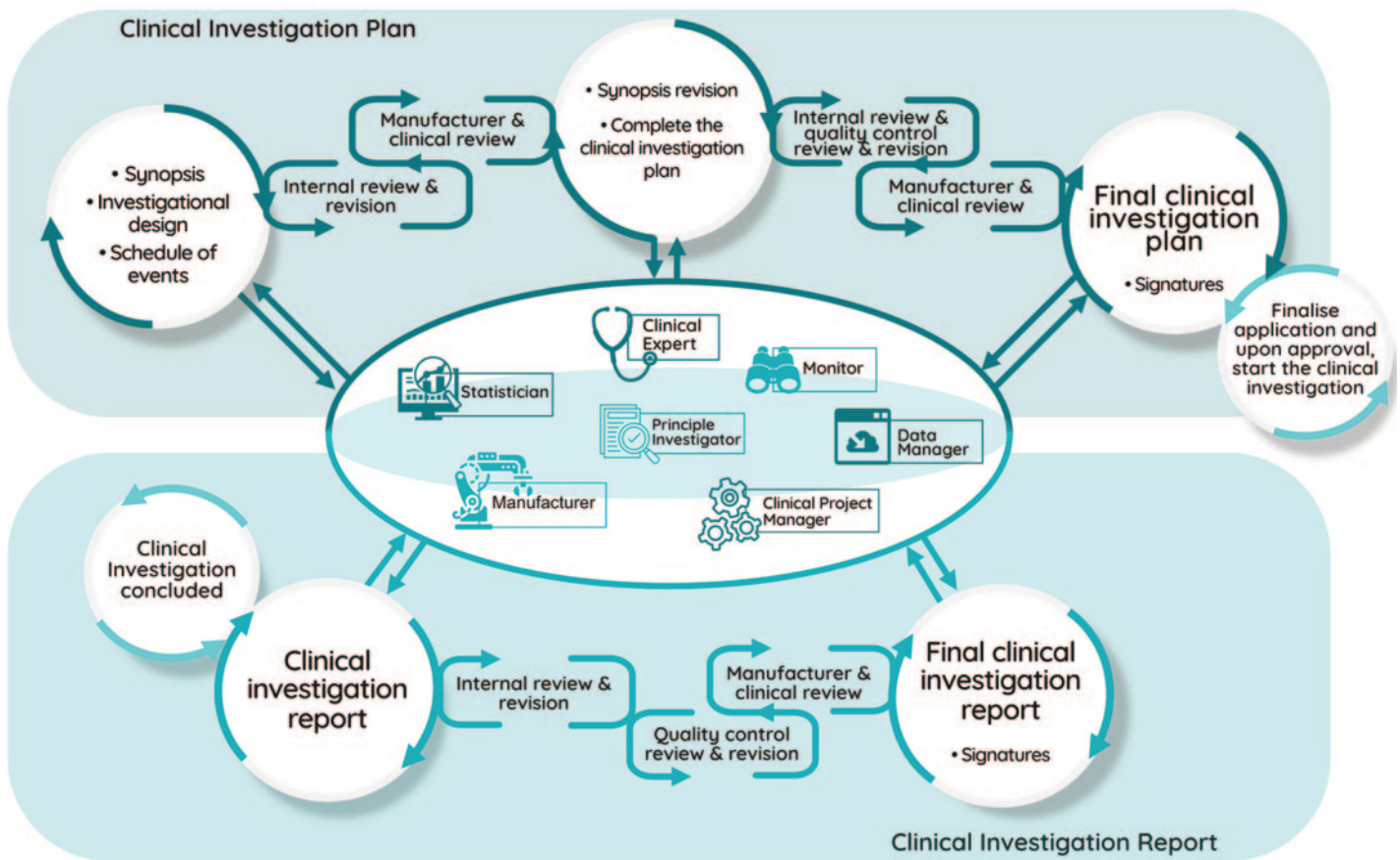
evaluation of residual risks. The requirements of what AEs must be reported, and within what timeframe, is an important difference between the two industries.<sup>4,6</sup>

**Clinical investigations may be less complex**

Although not directly affecting the study/investigational documentation, it's good to be aware that clinical investigations are often less complex than clinical trials and more adapted to the type of product. In the pharmaceutical industry, a standardised set of studies are typically required, from phase I in a small number of healthy volunteers or in some cases severely ill



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**Figure 3. Planning and collaboration example for writing CIPs and CIRs.**

An example on how the planning for writing a CIP (upper panel) and a CIR (lower panel) could look like is depicted, as well as who you as a medical writer might collaborate with.

patients, to phase IV post-marketing studies. Clinical investigations are adapted depending on risk class and intended purpose, and one single clinical investigation may be sufficient if it provides clinical data that support all claims stated for the product.

**Planning your work**

When planning the writing to meet set deadlines, make sure to include enough time to get answers to your questions from the investigational team and experts, for reviews and revisions, and for juggling other projects on the side. No matter if you work at a consultancy company like me, freelance as a medical writer, or are employed by a manufacturer, it's good to involve the manufacturer, colleagues, and experts early in the drafting of a CIP. Exactly how this may look will vary depending on your work situation, experience, and specified assignment. An example of a plan for writing a CIP and CIR, and

who you might collaborate with, is depicted in Figure 3.

**Start with the synopsis**

When writing a CIP, I suggest to first prepare a draft of the synopsis and have that thoroughly reviewed before drafting the CIP in its entirety. This can save a lot of time by not needing to update the document in several places multiple times, as most questions and discussions will be in relation to the synopsis, and all content of the synopsis (the CIP summary) will appear also in the main document. Personally, I like to include the full section on investigational design in this first draft, including the figure on overall investigational design and the schedule of events

It's important to have the synopsis and investigational design, and later the full CIP, reviewed by people with various professions and expertise to catch potential problems with the plan as early as possible, and to ensure that the plan is practically feasible.

table. I do this since they often spark discussion and, together with the synopsis, they set the basis for the CIP.

**It's teamwork**

It's important to include the coordinating/ principal investigator and any other medical expert as early as possible when drafting the synopsis to

obtain input on clinical investigational design and study procedures, and to ensure an appropriate study setup as close to standard clinical practice as possible. Access to a medical expert with relevant knowledge for the investigation is required according to ISO 14155.<sup>4</sup> The medical expert should be available to advise on the design of the investigation and to answer related medical



questions. Make sure to discuss any specific questions immediately with the clinician, or other concerned professionals (e.g., the investigation's statistician) or to discuss more general concerns with someone familiar with the project.

It's important to have the synopsis and investigational design, and later the full CIP, reviewed by people with various professions and expertise to catch potential problems with the plan as early as possible, and to ensure that the plan is practically feasible. If possible, to cover all theoretical and practical aspects, this should include a statistician, a monitor, and a data manager in addition to the clinical project manager, manufacturer, and the coordinating investigator. Depending on your own experience, you may also want to include someone more senior with regulatory knowledge.

Once the clinical investigation and the statistical report are finalised and you are ready to compile the CIR, make sure to clear out any questions regarding the statistical analysis with the statistician. While writing the CIR, you may also need to communicate with the data manager, monitor, and clinical project manager, depending on the project. The final CIR should be reviewed by the PIs and the manufacturer.

### Your role as a medical writer

As already discussed, designing a clinical investigation and writing a CIP and CIR is a collaboration involving many professionals with various expertise. Everybody contributes with their knowledge, including you. As you will write the documents, it's crucial that you fully understand the objectives, endpoints, and methodology of the investigation. To do that you will need to communicate with people of other professions.

If you have written these types of documents before, either for pharmaceuticals or for medical devices, you will have gained experience in study design and can make a valuable contribution. But even if this is your first time writing a CIP or CIR, more than likely you still have valuable experience and a different perspective from the rest of the team that would be useful. Perhaps you have other medical writing experience, or experience from designing laboratory experiments, that can be applied. Hence, do not be afraid to suggest alterations or to ask questions when something is unclear. Your role as a medical writer may differ depending on your work

situation and requested support. Independently, you will be responsible for conveying the core ideas of the investigation, providing necessary information according to applicable regulations and guidelines, and for coordinating comments and creating consistency throughout the documents.

### Conclusions

Writing CIPs and CIRs for medical devices is not very different from preparing corresponding documentation for the pharmaceutical industry. The most important is to follow applicable guidelines, use correct terminology, and be aware of certain differences such as safety reporting and its timelines. To get started writing CIPs and CIRs, read up on applicable guidelines, start with the synopsis, believe in your abilities, and don't be afraid to ask questions and provide input. Remember, preparing study documents is a collaboration.

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### Disclaimers

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### Disclosures and conflicts of interest

The author declares no conflict of interest.

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# Clinical evaluation reports: 6 years after the introduction of MEDDEV 2.7/1 revision 4

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## Abstract

MEDDEV 2.7/1 is the European guideline about the clinical evaluation of medical devices. The 4th revision, in 2016, updated how clinical evaluation should be conducted and reported, thus paving the way for clinical evaluation under the Medical Device Regulation (MDR) 2017/745. Transitioning directly from MEDDEV 2.7/1 revision 3 to the MDR would have been a huge leap; revision 4 has provided a stepping stone along the way to the MDR. This article considers how clinical evaluation and clinical evaluation reports (CERs) have evolved since 2016 and why MEDDEV 2.7/1 revision 4 is still in use today.

**M**EDDEV 2.7/1 is the European guideline about the clinical evaluation of medical devices. The 4th revision, in 2016, updated how clinical evaluation should be conducted and the main changes are described in this article. The implementation of the Medical Device Regulation (MDR) 2017/745 has brought further changes in how clinical evaluation is conducted and these are also described.

## MEDDEV 2.7/1 Rev. 4 (2016)

The European guideline MEDDEV 2.7/1 rev. 4, introduced in 2016,<sup>1</sup> updated the clinical evaluation process for medical devices. This revision confirms that clinical evaluation is a planned, continuous, and iterative process throughout the life cycle of a medical device. Guidance is provided on how to conduct clinical evaluation, including how to identify, appraise, and analyse clinical data; demonstrate equivalence to other medical devices; conduct literature reviews; and structure a clinical evaluation report (CER).

The main changes however, between revisions 3 and 4 of the MEDDEV 2.7/1 guideline, are the introduction of the clinical evaluation plan (CEP), expanding the current knowledge and determining the state of the art, and providing more detailed methods for conducting literature reviews (LRs). In practice, revision 4 made it more difficult to claim equivalence to other marketed medical devices (also known as predicate devices), as it put more emphasis on the need for clinical investigations, which aligns with the MDR 2017/745 requirements. These changes are discussed in more detail below.

**Clinical evaluation plan:** Before MEDDEV 2.7/1 rev. 4 was introduced, clinical evaluation

comprised three stages, namely, the identification, appraisal, and analysis of clinical data.<sup>2</sup> Revision 4 introduced an additional stage, Stage 0, that defined the scope and planning of the clinical evaluation. Before revision 4, CERs were produced when required and summarised the clinical evidence available up to that point in time. Therefore, the introduction of the CEP was a significant change in the clinical evaluation process.

The CEP sets out the scope of the clinical evaluation based on the Essential Requirements that need to be met. Note that Essential Requirements have been superseded by General Safety and Performance Requirements in the MDR. In the same way that a protocol or clinical



**Box 1. Changes to clinical evaluation introduced by MEDDEV 2.7/1 revision 4:**

- Introduction of the clinical evaluation plan;
- Expanded current knowledge section and determination of the state of the art in the CER;
- Objective literature review methodology;
- More difficulty claiming equivalence to other medical devices; and
- Increased emphasis on clinical investigations.

investigation plan describes how a clinical trial or investigation will be conducted, the CEP sets out how a clinical evaluation will be performed. It describes the medical device being evaluated,

including its indication, intended purpose, contraindications, warnings, and any design changes; information on equivalence to other medical devices (if claimed); the current knowledge and state of the art; sources and types of clinical data, including newly generated data to be used in the evaluation; and post-market surveillance (PMS) activities, including post-market clinical follow-up (PMCF). The CEP is used to determine what data are available; if there are any gaps in the data – and if so, how and when these gaps will be filled; and whether the data are suitable for evaluation. The CEP is reviewed and updated regularly, and in particular, before generating a CER. The CEP evolves as the medical device progresses through its life cycle and remains in use even after the initial conformity assessment and CE-marking. (See section 7 of the MEDDEV 2.7/1 rev. 4 for more guidance on scoping of the clinical evaluation and CEP content.)

**Current knowledge and state of the art:** What disease is the medical device intended to treat? How is this condition currently treated? For example, are there other medical devices, surgical, pharmaceutical, or non-medical treatments in use? Which treatments are suitable for which patients? Are there any problems or unmet clinical needs with currently available treatments? What treatments are in development? All of these questions, and more, should be addressed in the current knowledge section, which is a broad description and assessment of the epidemiology of the disease being treated and its diagnosis and pathology, including disease classification; treatment guidelines; and objectives and endpoints used in clinical investigations. Having reviewed all of this information the current state of the art is determined. The state of the art embodies what is currently and generally accepted as good practice in technology and medicine; it is not necessarily the most technologically advanced solution.<sup>3</sup>

MEDDEV 2.7/1 rev. 4 expanded and placed more importance on the current knowledge part of the clinical evaluation and determination of the state of the art. It plays an essential role in determining the development strategy of a medical device and features prominently in both the CEP and CER. For the medical writer, considerably more time is now required to write the current knowledge and state of the art sections of the CEP and CER.

In practice, revision 4 made it more difficult to claim equivalence to other marketed medical devices (also known as predicate devices), as it laid more emphasis on the need for clinical investigations, which aligns with the MDR 2017/745 requirements.

**Literature review:** That LRs should be based on an objective research question, conducted systematically, have a literature search protocol, and generate a search report was stated in MEDDEV 2.7/1 rev. 3 and reiterated in rev. 4. Note that the guidelines refer to “the literature review”, suggesting that only one LR protocol, search strategy, search report, and LR are required. In practice, because the literature search needs to be tailored to the purpose of the LR more than one literature search is required. Therefore, to identify appropriate literature for the current knowledge and state of the art sections and the device under evaluation or equivalent device (if claiming equivalence), separate protocols, strategies, and search outputs are required. Additional literature searches may also be performed to support PMS activities.

Individual articles about the device under evaluation (or equivalent device) are appraised,





i.e., assessed for their weighted contribution to the evaluation of clinical safety and performance in a methodological and documented way. MEDDEV 2.7/1 rev. 4 does not give any examples of appraisal methods, but it does refer to the widely used Appendix D from the Global Harmonization Task Force (GHTF) clinical evaluation guideline,<sup>4</sup> now Appendix F in the updated International Medical Device Regulators Forum (IMDRF) guideline.<sup>5</sup> Once appraised, articles to be included in the clinical literature about the device under evaluation are presented in a data extraction table, summarised, and analysed. Narratives of individual literature reports disappeared with the introduction of MEDDEV 2.7/1 rev. 4. Instead, an overall critical and objective analysis of the literature is expected, which in turn contributes to the assessment of clinical safety and performance.

**Equivalence:** Claiming equivalence to another medical device became much more difficult with

the introduction of MEDDEV 2.7/1 rev. 4 and the MDR. Not only did the strict criteria for clinical, technical, and biological equivalence have to be fulfilled, but for class III devices in particular, access to the technical file and a contract with the manufacturer of the equivalent device are now also required.

**Clinical investigations:** There was always a requirement for clinical investigations for class III and implantable medical devices and for devices where gaps in clinical data could not be filled in other ways. As MEDDEV 2.7/1 rev. 4 has made claiming equivalence to other devices increasingly difficult, more clinical data now needs to be generated from clinical investigations.

#### Medical Device Regulation 2017/745

As a consequence of the pandemic, the transition to the MDR<sup>6</sup> was delayed by a year until May 2021. Thus manufacturers and notified bodies had 5 years from the introduction of MEDDEV

2.7/1 rev. 4 to adapt their practices and prepare for the MDR. In addition to the changes in clinical evaluation already described, the MDR placed more emphasis on risk assessment, especially benefit-risk analysis, and the need to show that the benefits attributed to a medical device were supported by data. It also reaffirmed the need for PMCF.

**Risk assessment:** Bringing together and analysing all clinical data is what clinical evaluation is

#### Box 2. Changes to clinical evaluation introduced by MDR 2017/745:

- More extensive risk assessment and benefit-risk analysis;
- Benefits identified and supported by data; and
- Importance of PMCF reaffirmed.



all about. Since the introduction of MEDDEV 2.7/1 rev. 4, this has become a much more extensive task that involves a benefit-risk analysis of the medical device. In the past, the focus was very much on the risks associated with the device, but the introduction of the MDR meant that the benefits of using the device also have to be demonstrated and all claims substantiated.

Although the CER table of contents in Appendix A9 of MEDDEV 2.7/1 rev. 4 is still followed, section 4.6 (Analysis of Clinical Data) often needs to be expanded and adapted to meet the requirements of the MDR.

**Post-market clinical follow-up:** There has always been a requirement for PMCF;<sup>7,8</sup> this is confirmed by MEDDEV 2.7/1 rev. 4 and reinforced by the MDR. Consequently, much more detail about PMCF studies is now expected in the PMS section of the CER with references to the PMCF plan and report.

## Conclusions

It has been 6 years since MEDDEV 2.7/1 rev. 4 was introduced and 1 year since the MDR came into force. Both have affected how clinical evaluation is conducted. Most notably, MEDDEV 2.7/1 rev. 4 introduced the CEP and emphasised that clinical evaluation is a continuous process and not just a report produced at intervals, and it also made equivalence a more difficult route to CE-marking. The MDR has expanded risk assessment, with more focus on the benefits of a medical device and more emphasis placed on PMCF.

For the medical writer, the CER is now closely linked to the CEP, which has a much more extensive current knowledge and state of the art sections; more objective and analytical LR; and more extensive risk assessment, PMS, and PMCF sections. As a result, CERs require more time to write (sometimes twice as much) than was the case with MEDDEV 2.7/1 rev. 3. However, the whole clinical evaluation process is now a much more planned, objective, robust, and comprehensive assessment than it used to be.

The MDR does not give guidance on how to perform clinical evaluation or how to write a CER. Consequently MEDDEV 2.7/1 rev. 4 is still very much in use today.

## Disclaimers

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

## Disclosures and conflicts of interest

The author declares no conflicts of interest.

## Data availability statement

N/A.

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# Post-market clinical follow-up insights

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## Post-market clinical follow-up in a nutshell

**P**ost-market clinical follow-up (PMCF) is part of post-market surveillance (PMS) and is the process of collecting clinical data to confirm the safety and performance of a CE-marked device during the device's lifetime after its market approval.<sup>1</sup> PMCF is similar to the post-approval studies for pharmaceuticals. The main difference from PMCF requirements under the EU Directive 93/42/EEC on Medical Devices (MDD) is the focus on PMCF as a continuous process. The PMCF plan describes the methods and procedures to collect clinical data, whereas the PMCF report describes and evaluates the results. These results potentially impact other documents, such as the clinical evaluation report (CER), the risk management file, and if

## Abstract

The EU Medical Devices Regulation (MDR) brought about new post-market clinical follow-up (PMCF) requirements for medical devices. Whereas complaint monitoring and literature searches were often sufficient under the Medical Devices Directives (MDD), a more proactive approach is now required. User surveys, data collection from registries, or PMCF studies are examples of how manufacturers can collect clinical data for CE-marked devices. All planned activities are documented in the PMCF plan, including a justification of the appropriateness of each activity. But what is appropriate for what type of device? In how much detail should the results be presented in the PMCF report without duplicating the information in the clinical evaluation report (CER)? This article shares experiences and discusses some case studies for different device types.



applicable, the Summary of Safety and Clinical Performance (SSCP).<sup>2</sup> The Medical Device Coordination Group (MDCG) published

The Medical Devices Coordination Group (MDCG) is an expert committee composed of persons designated by the Member States based on their role and expertise in the field of medical devices. The MDCG “deals with key issues from the medical devices sector, from Notified Body oversight or standardisation to market surveillance, passing by international matters, new technologies, and clinical investigation”.<sup>3</sup>

templates for both the PMCF plan and report in April 2020 to guide manufacturers.<sup>4,5</sup>

Articles on new documents under Medical Devices Regulation (MDR) 2017/745 and general principles of PMCF are shown in Box 1.

### PMCF plan and report

Guidance on how to set out the PMCF plan is given in MDCG 2020-7.<sup>4</sup> The PMCF plan is part of the PMS plan and of the clinical evaluation plan (CEP). The aim of the PMCF plan is to:

- Confirm the safety and performance, including the clinical benefit if applicable, of the device throughout its expected functioning lifetime.
- Identify previously unknown side-effects and monitor the identified side-effects and contraindications.
- Identify and analyse emergent risks on the basis of factual evidence.
- Ensure the continued acceptability of the benefit-risk ratio, in accordance with Annex I in the MDR.
- Identify possible systematic misuse or off-label use of the device; to verify that the intended purpose is correct.

The seven sections of the PMCF plan are shown in Box 2.

Guidance on how to set up the PMCF evaluation report are presented in MDCG 2020-8.<sup>5</sup> As might be expected, the PMCF report layout is very similar to that of the PMCF plan. The main difference is that the PMCF report focuses on presenting and evaluating the results of PMCF and determining the impact on the technical documentation. The sections of the PMCF report are listed in Box 3. The PMCF report is part of the CER and technical documentation. The conclusions of the PMCF report are used to update the clinical evaluation, risk management documentation, the PMS plan and, if applicable, the SSCP. Therefore, it is important to schedule the PMCF report to make the results and conclusions available for inclusion in these documents. This requires careful planning for class III devices with annual CER updates. How much detail the PMCF report should provide remains a matter of debate. It seems unnecessary to repeat the information from the PMCF report one by one in the CER. Some manufacturers only summarise the results from literature searches, surveys, and other PMCF activities in the PMCF report and analyse the results in more detail in

#### Box 1. Recommendations for further reading

For general information about new documents under MDR and principles of PMCF, the following articles are recommended:

- Bhatia P, Collada Ali LC, Goodwin Burri K, et al. New documents required by the medical device regulation. *Medical Writing*. 2020; 29(3):24–9.
- Collada Ali LC, Friedrich KJ. First experiences writing summaries of safety and clinical performance for medical devices. *Medical Writing*. 2020; 29(4):62–5.
- Doerr B, Whimtan S, Walker S. Medical Devices Writing for medical devices compared to pharmaceuticals: An introduction Authors. 2017; 26(2):8–13
- Römermann K, Theilmann W. Post-market clinical follow-up plans and evaluation reports. *Medical Writing*. 2020;29(4):83–4

#### Box 2. PMCF plan template – sections

- A. Manufacturer contact details
- B. Medical device description and specification
- C. Activities related to PMCF: general and specific methods and procedures
- D. Reference to the relevant parts of the technical documentation
- E. Evaluation of clinical data relating to equivalent or similar devices
- F. Reference to any applicable common specification(s), harmonized standard(s) or applicable guidance document(s)
- G. Estimated date of the PMCF evaluation report

Source: MDCG 2020-7

### Box 3. PMCF evaluation report template – sections

- A. Manufacturer contact details
- B. Medical device description and specification
- C. Activities undertaken related to PMCF: results
- D. Evaluation of clinical data relating to equivalent or similar devices
- E. Impact of the results on the technical documentation
- F. Reference to any common specification(s), harmonised standard(s), or guidance document(s) applied
- G. Conclusions

Source: MDCG 2020-8

### Box 4. Hierarchy of clinical evidence for confirmation of conformity with GSPRs under MDR

1. Results of high quality clinical investigations covering all device variants, indications, patient populations, duration of treatment effect, etc
2. Results of high quality clinical investigations with some gaps
3. Outcomes from high quality clinical data collection systems such as registries
4. Outcomes from studies with potential methodological flaws but where data can still be quantified and acceptability justified
5. Equivalence data (reliable/quantifiable)
6. Evaluation of state of the art, including evaluation of clinical data from similar devices
7. Complaints and vigilance data; curated data
8. Proactive PMS data, such as that derived from surveys
9. Individual case reports on the subject device
10. Compliance to non-clinical elements of common specifications considered relevant to device safety and performance
11. Simulated use/animal/cadaveric testing involving healthcare professionals or other end users  
Pre-clinical and bench testing/compliance to standards

GSPR = General Safety and Performance Requirements. Source: MDCG 2020-6 Appendix III

the CER. However, this can result in duplication of effort, especially when the CER is not written immediately after the PMCF report. Therefore, a complete analysis and appraisal in the PMCF report with a summary of the results in the CER might be the better choice.

### PMCF data collection – When and what to do

The first step in planning PMCF activities is to identify any gaps in the clinical evidence of a device. The clinical evaluation should analyse whether all claims are supported. If not, the PMCF plan describes how identified gaps can be closed. This might involve gathering clinical data. Examples of clinical data sources include:

- **Literature screening** which is one of the easiest methods of collecting clinical data. The PMCF plan should include a specific and objective research question and there should be a detailed literature search protocol. Reviewing case reports is a good way of identifying possible off-label use or misuse.
- **Post-market studies** can have different designs, such as extended follow-up of a pre-market investigation, a new clinical investigation, or a retrospective study. The PMCF plan should include the proposed study design, sample size, endpoints, inclusion/exclusion criteria, and a statistical rationale. Evidence from post-market studies is usually expected for implantable devices and class III devices.

- **Manufacturer or national public registries** on the device or the device group can be a good source of real-world clinical evidence. If a new registry is initiated, the PMCF plan should include a description of the registry and a preliminary specification of the expected quantity and quality of the data. A new, manufacturer-initiated registry has the advantage of being device-specific but will not contain historic data and will take time to accumulate data on a large number of patients over a long period. However, an existing national registry can be very useful if it contains historic data on similar devices from a large patient population, but has the disadvantage of not being device-specific.
- **Commercial data sets collected from electronic health records** are provided by companies that gather, process, and analyse health data from international and local markets. These data sets can include information about patient feedback, product performance, or competitors, among others.
- **Surveys**, especially when distributed online, can be good way of quickly reaching large numbers of patients or healthcare professionals. Like post-market studies, user surveys should be based on a predefined endpoint and statistical rationale.
- **Social media listening** allows for monitoring of patients' opinions on a given device as stated publicly through social media or other online means.<sup>6</sup>

All of these tools can be used to collect post-market data, but a certain level of clinical evidence is required depending on the device class, risk profile, and marketing history.

### What is “sufficient clinical data”?

Clinical data is information concerning safety or performance that is generated from the use of a device. This information can be sourced from clinical investigations of the device or equivalent devices, published peer reviewed literature about the device or equivalent devices, or clinically relevant information from PMS – especially PMCF.<sup>7</sup>

Clinical data is needed to:

- Confirm compliance with the applicable general safety and performance requirements (GSPRs) according to MDR Annex I.<sup>1</sup>
- Evaluate undesirable side effects and the acceptability of the benefit-risk ratio.

The clinical evaluation includes a thorough and objective assessment of both favourable and unfavourable clinical data that forms the clinical evidence for a device.<sup>8</sup> PMCF is required for all devices (new and legacy), but, current guidelines focus on legacy devices as this affects all manufacturers. However, MDR 2017/745 is often vague on when clinical data are considered “sufficient”. To rectify this situation, the MDCG endorsed a guidance document in accordance with Article 105 of the MDR<sup>9</sup>: [MDCG 2020-6 “Regulation \(EU\) 2017/745: Clinical evidence](#)





needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC – A guide for manufacturers and notified bodies”.<sup>10</sup>

This guideline sets out the clinical data requirements for a legacy device to demonstrate conformity with the MDR.

Legacy devices are existing devices that have already been placed on the market under EU Directive 93/42/EEC on MDD or Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) before the MDR came into force.

The MDR defines clinical evidence as the “clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer”. However, “sufficient” is not defined in the MDR. MDR Article 61 also mentions that conformity with the relevant GSPR shall be based on sufficient clinical evidence.<sup>1</sup> Therefore, “sufficient clinical evidence” is understood as “the present result of the qualified assessment which has reached the conclusion that the device is safe and achieves the intended benefits”.<sup>1</sup> It is important to note that clinical evaluation is a process where this qualified assessment has to be done continuously.

The MDCG 2020-6 (Appendix III) develops the concept of a hierarchy of clinical evidence, ranked roughly in order from strongest to weakest; variations may apply depending on the device for which GSPR evidence is required and the quality

of individual data sources.<sup>10</sup>

The strongest evidence are the results of high-quality clinical investigations covering all device variants, indications, patient populations, duration of treatment effect, etc. On the contrary, the weakest evidence are pre-clinical and bench testing / compliance to standards. (See Box 4 on p. 46.) Class III legacy and implantable legacy devices are technologies that are not well-established and should have at least Level 4 clinical data. Well-established technologies may be able to confirm conformity with GSPRs using cumulative evidence from Levels 5 to 12; they cannot rely only on complaints and vigilance data.

Well-established technologies have to meet the following criteria:

- relatively simple, common and stable designs with little evolution;
- their generic device group is known to be safe and has not been associated with safety issues in the past;
- well-known clinical performance characteristics and their generic device group are standard of care devices with little evolution in indications and the state of the art;
- a long history on the market.<sup>10</sup>

### Practical considerations

Medical writers are often involved in planning PMCF activities. Table 1 describes different fictional medical devices and examples of how clinical data might be collected.

In conclusion, the MDR brought about new post-market clinical follow-up (PMCF) requirements for medical devices and a more active approach is now required. There are several ways of fulfilling this requirement, such as user

surveys, data collection from registries, or PMCF studies, web listening and commercial electronic health records databases. All planned activities are documented in the PMCF plan, and the results of these activities need to be presented in the PMCF report without duplicating the information that will subsequently be presented in the CER.

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### Disclaimers

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### Disclosures and conflicts of interest

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2. Collada Ali LC, Friedrich KJ. First

**Table 1. Examples of PMCF activities per device type**

Device description	PMCF activities suggested
<p><b>An implantable device with new technology:</b> This is a class III device used in cardiovascular surgery in combination with pacemakers. The device was recently CE-marked. The clinical evidence derives from a pre-market clinical investigation with a follow-up of 36 months.</p>	<p><b>Example 1: Extended follow-up of the pre-market clinical investigation</b> As an implantable device used in cardiovascular surgery, notified bodies will expect a longer follow-up (e.g., up to 5 years) to provide evidence on the long-term safety.</p>
	<p><b>Example 2: Manufacturer-initiated registry</b> PMCF is a continuous process. Once a registry has been set up, long-term data collection is possible.</p>
<p><b>Well-established device (First example)</b> A common example of a well-established device is a prosthesis (hip, knee, etc.) which has been on the market for more than 20 years.</p>	<p><b>Example 1: Local and international registries</b> There are many registries which collect data on all implanted prostheses and produce yearly reports summarizing those data. These are a real-world means of analysing performance and safety of a particular prosthesis.</p>
	<p><b>Example 2: Social media listening</b> Patients may express their views, good and bad, on social media after having a prosthesis implanted. Web listening may help in getting patients' opinions on a given device.</p>
<p><b>Well-established device (Second example)</b> Screws and plates are typical examples of well-established technologies mentioned in the MDR.</p>	<p><b>Data collection from electronic health records</b> Manufacturers can pay for electronic health records to receive data sets about adverse events, patient feedback data, social media reporting, etc.</p>
<p><b>Low-risk device</b> An example of a low risk device is a sterile wound dressing.</p>	<p><b>Example 1: User survey</b> Inviting patients and health care professionals to give feedback by completing an online survey.</p>
	<p><b>Example 2: Social media listening</b> Users may express their views on social media.</p>

experiences writing summaries of safety and clinical performance for medical devices. *Med Writ.* 2020;29(4):62–5

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Pros	Cons
The previous study protocol, including endpoints and inclusion/exclusion criteria, can be used to develop a follow-up study. This requires less effort to set up than a new clinical investigation.	The longer the study the more likely it is that patients will be lost to follow-up which can affect the validity of the results.
Registries are one of the best ways of continuously collecting real-world clinical data.	Initiating a registry requires time and money, and appropriate endpoints. The register needs to be well maintained to generate high-quality data.
Registries contain an impressive amount of data and represent real-life cases on all prostheses, including competitors' devices. This is useful when comparing safety and performance data across different devices and over the long term.	Different registries may present data in different ways and formats and analysing all data together may be challenging. Annual reports are created for some registries. However, not all registries are publicly accessible.
These data are not influenced by the manufacturer. However, negative results are likely to be reported more frequently than positive results.	Data can be difficult and cumbersome to collect. Continuous monitoring is needed. May not be easy to analyse all data together. A per case analysis may be needed.
Data from scientific literature or from clinical investigations is often limited for these devices. Electronic health records are an option to collect safety and performance data for devices with a long market history.	Unambiguous identification of a device may be difficult before unique device identifiers (UDI) have been adopted. Data sets have to include information relevant to the safety and performance parameters of a device. This might not be possible depending on the device and the information available.
A well-structured online survey can quickly generate useful data.	Not all users will complete the survey so data may be incomplete and not representative of all users.
Data are supposedly unbiased as they are not directly requested by the manufacturer. However, negative results are likely to be reported more frequently than positive results.	Continuous monitoring is required. Unsolicited information can be difficult to collate and analyse. If the device is low risk, and also well-established, there may be very few comments.



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Device Coordination Group (MDCG) are drafted in collaboration with many parties and aim at implementing a common understanding of the legislation and increased harmonisation of documents in the medical device industry.<sup>10</sup> The European Commission (EC) has been working for several years on a guidance to assist manufacturers in creating PSURs compliant to the MDR. Nonetheless, up until now, only drafts have been shared to collect comments, and the guidance on the PSUR is still showing as “MDCG work in progress” on the EC’s website

even though the expected date of MDCG endorsement is listed as Q4-2021.<sup>10</sup> MDCG guidances are not legally binding<sup>10</sup> but are used as reference documents (checklists) by NBs to review and audit, thus, are incredibly relevant. Quite concerning is that the first PSURs for class IIb (including implantables) and class III devices are due on May 26, 2022, 1 year after DoA. At the time of writing, the medical device sector and the NBs do not have an “official guidance” as a reference and cannot expect manufacturers to follow the MDCG PSUR draft guidance to the

letter. Consequently, it is highly recommended to have regular conversations and agreements with the NBs regarding submissions and content of the PSURs.

Several draft versions of the PSUR guidance have been circulated since 2020, and what started as a lean, high-level document has evolved into a very dense, intricate, and extensive manuscript, still unclear and ambiguous in certain sections. The draft guidance breaks down what is shown in Table 1 in more detail. It provides more information on what CAPAs to present in the

**Table 1. PSUR and PMSR requirements and differences by device class according to EU MDR**

Report	PMSR (low-risk devices)	PSUR (medium to high-risk devices)	
Device class MDR	Class I	Class IIa	IIb and III
		Class IIa and IIb implantables	
Periodic update cycle	As needed, determined by the manufacturer	At least every 2 years	yearly
Common requirements	Results and conclusions of the analyses of the post market surveillance data gathered as a result of the post market surveillance plan referred to in Article 84		
	Rationale and description of any preventive and corrective actions taken		
Specific requirements based on MDR Articles 84, 85, 86, and Annex III	Complaint handling and AE reporting (vigilance): serious incidents and non-serious incidents (Art. 88)		
	Recalls and field safety notices		
	Scientific and technical literature. If applicable, based on the class and type of the device		
	Customer feedback and other proactive PMS activities (e.g., satisfaction survey, user survey, social media listening, focus groups, expert panels, etc.). If applicable, based on the class and type of the device		
		<ul style="list-style-type: none"> <li>Information on similar devices from AE and FSCA databases (e.g., MAUDE, MHRA, IMDD, etc.)</li> <li>Registries (e.g., National Joint Arthroplasty Registries, etc.)</li> <li>Main findings of the PMCF activities (e.g., specific literature, hospital registries, patient databases, specific clinical customer surveys, PMCF studies, etc.)</li> <li>The volume of sales of the device and an estimated evaluation of the size and other characteristics of the population using the device and, where practicable, the usage frequency of the device</li> <li>Conclusions of the benefit-risk determination</li> </ul>	
Regulatory requirements	To be maintained and available to EU competent authorities upon request, but it does not need to be submitted regularly	The PSUR for Class III and implantable medical devices must be submitted via EUDAMED	

Abbreviations: AE, adverse event; EUDAMED, European Database for Medical Devices; FSCA, field safety corrective action; MAUDE, Manufacturer and User Facility Device Experience; MHRA, Medicines and Healthcare products Regulatory Agency; IMDD, Investigational Medical Device Dossier; PMCF, post market clinical follow-up; PMS, post market surveillance

**Table 2. Overview of the MDCG PSUR draft guidance and associated challenges**

Topic	Content	Additional Details & Challenges
<b>Executive summary</b>	Background information related to the benefit-risk profile	<ul style="list-style-type: none"> <li>• If applicable, brief status description of actions taken by the manufacturer in the previous PSUR</li> <li>• If applicable, brief status description of the action taken by NBs in the previous PSUR</li> <li>• Data collection period</li> <li>• Based on the main results of the current PSUR, a clear statement indicating if the benefit-risk statement has been impacted positively or negatively</li> </ul>
<b>Description</b>	General	Device classification, CE date (or first availability in the market), the status of the device in the market, intended purpose (instructions for use), indications, contraindications & target population
	MDR devices (BUDI-DIs)	Information provided according to BUDI-DIs groups, outlining device changes within the groups compared to previous PSURs, if applicable.
	Legacy devices & custom-made devices	Information provided by device model/device groups
<b>Grouping of the devices</b>	Grouping rules and additional considerations	<ul style="list-style-type: none"> <li>• Multiple BUDI-DIs (or device families) may be covered in one PSUR as long as they have the same NB</li> <li>• In case the device is marketed with successive certificates of different NBs, a cross-reference should be added in the PSUR</li> <li>• In case of Multiple BUDI-DIs, performance should be clearly identified per BUDI-DI group</li> <li>• Introduction of “leading” device and “secondary” device concepts and changes in “leading” device</li> </ul> <p><b>Challenges</b></p> <ul style="list-style-type: none"> <li>• In case a PSUR includes several BUDI-DIs, the data must be presented in a way that the performance of each BUDI-DI can be followed.</li> <li>• Can become very complex depending on the manufacturer portfolio and number of medical devices</li> </ul>
<b>Sales volume</b>	Volumes of sales, units shipped, or units implanted or another suitable method	<p>All devices placed on the market, presented in a yearly format, providing devices information (sizes, models &amp; configurations)</p> <p><b>Challenges</b></p> <ul style="list-style-type: none"> <li>• To determine sales or shipments for multiple-use instruments can be challenging since many instruments are supplied in loner kits (directly sent to the hospital and then returned to the manufacturer). For example, an alternative is to use implant sales as a reference to indicate the number of surgeries.</li> </ul>
<b>Size and other characteristics of the population using the device</b>	The population for which the device has been used considering the device claimed intended purpose	<p>Reported on the extent which is possible for the manufacturer</p> <p><b>Challenges</b></p> <ul style="list-style-type: none"> <li>• The size and characteristics of the actual population using the device are often tough to obtain. Patient information is sensitive and can only be shared on a high-level basis. Also, the hospital/ surgeon usually does not report such information.</li> </ul>

PSUR, the grouping of the devices, PMS requirements for medical devices remaining under Medical Device Directives, until when a PSUR is required (i.e., device lifetime), data collection periods, subsequent updates of the PSUR, and finally regulatory aspects (e.g. timelines, and submission to the European Database for Medical Devices [EUDAMED] and in the absence of EUDAMED).<sup>11</sup> Also, six annexes with additional information such as a content checklist, additional information on requirements, data reporting, data evaluation and

submission, terminology, and a PSUR form to be filled for EUDAMED submissions are part of the draft. One of those annexes suggests ways of presenting data in several proposed table templates, all of which make evident how time-consuming authoring a PSUR according to this guidance will be and the probable expectations of regulatory bodies. Table 2 summarises the content of the MDCG PSUR requirements based on last year’s draft<sup>11</sup> and the main associated challenges from the authors’ perspective.

**Associated challenges**

In agreement with Ben-Menaheem et al. 2020, the MDR brings substantial improvement to patient safety by consolidating the requirements on vigilance and PMS, clinical investigations, conformity assessments and adds significant changes to the roles of NBs in terms of audits and certifications.<sup>12</sup> It emphasises a more rigorous risk management process by establishing a stronger relationship between the clinical evaluation and PMS processes. Nevertheless, it also introduces several layers of complexity

Table 2. Continued

Topic	Content	Additional Details & Challenges
Post Market Surveillance (PMS) data including general PMCF data	Vigilance data	<ul style="list-style-type: none"> <li>Complaints and statistical analyses (trend reports)</li> <li>Serious Incidents reported to competent authorities</li> <li>Non-serious incidents (Article 88 trend report)</li> <li>IMDRF AE terminology</li> </ul> <p><b>Challenges</b></p> <ul style="list-style-type: none"> <li>No guidelines or instructions are given on which statistical tools to be used for the trend analysis</li> <li>Trending on IMDRF data might be challenging if not enough historical data is available</li> <li>No templates or guidelines given on how to perform the trending according to Article 88</li> </ul>
	General PMCF data	<ul style="list-style-type: none"> <li>Complaints: not reported in the vigilance section, IMDRF grouped or by internal event code, occurrence rates, justification for the exclusion of complaints</li> <li>Scientific literature review, public registry data, public information on similar devices, other</li> </ul> <p><b>Challenges</b></p> <ul style="list-style-type: none"> <li>For example, most national joint registries only collect data on hip and knee arthroplasty implants. Only a couple collect data on other anatomical joints like shoulder, wrist, ankle, etc.</li> <li>Many registries have incomplete data and cannot provide special reports to industry</li> <li>AEs identified in literature is challenging because product information is extremely limited or not available. Consequently, a proper investigation is hardly possible. Also, potential duplication of complaints may occur.</li> </ul>
	Preventive or corrective actions (Article 83.4)	<ul style="list-style-type: none"> <li>CAPAs resulting from the PMS system</li> <li>Quality management system related (CAPAs are excluded) unless they could have a direct impact on product safety, performance, or quality</li> </ul> <p><b>Challenges</b></p> <ul style="list-style-type: none"> <li>Every CAPA can somehow directly impact product safety, performance, or quality. It is difficult to determine which CAPAs can be excluded.</li> </ul>
	Preventive and corrective actions for safety reasons	(FSCA, Article 87) FSCAs resulting from the PMS system
Specific Post Market Clinical Follow-up (PMCF) data	Summary of data generated from PMCF activities	<ul style="list-style-type: none"> <li>Data not limited to PMCF studies, may include but not limited to, evaluation of suitable registers, manufacturer device registries, surveys, and real-world evidence analyses</li> <li>PMCF Report may be referred to, but enough details should be outlined in the PSUR</li> </ul> <p><b>Challenges</b></p> <ul style="list-style-type: none"> <li>Surveys might not provide specific enough information/ adverse events</li> </ul>
Summary of the findings and conclusion of the PSUR	Data validity, overall conclusion and, if applicable, action(s) taken by the manufacturer	<ul style="list-style-type: none"> <li>Data limitations</li> <li>If applicable, newly identified risks and their potential clinical impact as well as new identified benefits</li> <li>A conclusion to determine if the benefit-risk profile has changed</li> <li>Specific actions taken to address any identified unknown risks</li> <li>Actions taken during the data collection period evaluated in the PSUR</li> </ul>

Abbreviations: NB, notified body; BUDI-DI, Basic Unique Device Identification – Device Identifier; AE, adverse event; IMDRF, International Medical Device Regulators Forum; CAPA, corrective and preventive actions; FSCA, field safety corrective actions

because not only do challenges related to the PSUR content exist (Table 2), but there are also numerous steps involved in its creation process. Some concrete examples are data retrieval, data processing, data analysis, data consistency and accuracy, development and sustainability of

proactive PMS activities, and building quality into the PSUR process. Furthermore, MDR requirements on PMS apply to “legacy” and “old” medical devices,<sup>13</sup> although some flexibility is allowed to create leaner documents for the latter. Also, if the “old” devices were not phased out

from the market before DoA, the conditions of the MDR apply.<sup>13</sup>

All of the conditions mentioned above increase compliance costs throughout new product development, certification, and maintenance while also relying heavily on the



availability of adequate resources. Large companies with large product portfolios may absorb those expenses. Still, many of those large companies were forced to re-evaluate their product portfolio based on their company size, number of marketed products, number of sales, number of countries where the medical devices are marketed, the volume of complaints, type of indication(s) for which the medical device is specified and more. In comparison, smaller companies and start-ups, which represent 95% of the medical-technology sector and are considered a vital source of progress and innovation, may not fare as well due to an increase in regulatory compliance costs and longer times to market for new medical devices, all resulting from the new MDR requirements.<sup>12</sup> Furthermore, the introduction of the MDR has served as an example for many non-EU countries, resulting in an update of their medical device regulations with more strict PMS requirements. As a result, companies have started to receive requests for PMS reports that may or not require the same content, thus adding to the current workload introduced by the MDR.

### Is automated report authoring the future?

An article published in 2019 on trends in regulatory writing<sup>14</sup> mentioned how PV

companies had recognised the importance of automation for data mining and artificial intelligence (AI) to address the volume of data availability, data collection cost, data assessment, data processing, and analysis. These aim to reduce execution time, labour cost, human error, increase consistency within the data and among different authors of documents. At the same time, the use of AI is left to the interpretation and analyses of data, thus moving towards predictive PV.<sup>14</sup> Currently, automation and AI are highly focused on retrieving and reviewing medical literature because it is considered a substantially time-consuming task. It involves developing consistent search strategies of scientific publications, their appraisal, the extraction of adverse events (AEs), and adequate analysis by subject matter experts (SMEs). However, a recent publication stressed<sup>15</sup> the utilisation of AI can go beyond data mining of literature to include analysis of safety data from various internal databases used within companies and external sources like AEs global databases or social media. The above aspects are also transferable to the medical device industry, specifically the automation of PSUR and PMSR authoring. Based on the content on the MDCG guidance on PSUR requirements, the author opines that companies should invest, especially those with large portfolios, in automating the

creation of PSURs and PMSRs. The aim would be to reduce lead times in writing the reports, decrease workload, increase the number of reports produced, and meet submission deadlines while maintaining content quality and compliance to the MDR and other applicable regulations. This would definitely have a beneficial business and cost impact.

Pianka et al. (2021) developed an electronic platform for PV that populates a periodic safety update template. One of their first steps was to identify automatable content versus non-automatable content. Automatable content was defined as information that could be authored by extracting data from source documents or internal company databases (e.g. sales, distribution data, statistical analyses, etc.), and non-automatable content was defined as information that required discussion and interpretation by SMEs (e.g. benefit-risk conclusion). The result was a combination of fully automated, semi-automated, and non-automated sections. The authors reported that automation saved 25% of the time required to write a safety update report and an overall quality improvement, which translated into cost savings.<sup>16</sup> PSUR and PMSR automation is undoubtedly the future for the medical device sector. Nonetheless, challenges, risks, and limitations should be considered such as cost-benefit, ensuring source data consistency, errors pulling source data, maintenance of the tool to keep with regulation changes, amongst many others.

### Conclusion and outlook

The MDR certainly improves patient safety. The PSUR and PMSR are undoubtedly some of its most effective tools to demonstrate cohesiveness among vigilance, PMS, clinical evaluation, risk processes, and regulatory bodies. Thus, they are crucial to determining benefit-risk profile changes. Challenges are inevitable whenever a new process is implemented for the first time because of the associated additional resources, workload, and high costs. This is also true for the first PSURs and PMSRs implementation, notably if data mining is involved. However, the constant re-drafting of the MDCG guidance on PSUR requirements without a final official version released to date poses additional hardships for manufacturers, especially when the first regulatory deadlines for PSUR readiness are around the corner. Furthermore, there is still lack of clarity in some sections of the draft due to certain complexities that can be interpreted



differently by manufacturers.

It is important not to underestimate the requirements of the PSUR. Future considerations should take into account proper resource planning (roles and responsibilities), adequate training of resources (an increase of expertise), metrics (number of late PSUR submissions, number of error and inconsistencies, audit observations, etc.), automation of data mining methods and the actual authoring of reports (reducing manual labour and human error) and finally clear and constant communication with the NB in terms of PSUR expectations and submissions (clarification of content and timelines).

### Disclaimers

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

### Disclosures and conflicts of interest

The author declares no conflicts of interest.

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# New rules for artificial intelligence in Europe

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## Abstract

The proposal for a European Artificial Intelligence Act is unsettling medical device manufacturers because it might change the risk assessment of their devices and cause additional efforts regarding vigilance and technical documentation. Conflicting regulations complicate the situation further. The proposal is currently being discussed and will be applicable at the earliest in the second half of 2024, providing time for further adjustments and clarification.

## New rules for artificial intelligence in Europe

**A**rtificial intelligence (AI) is considered the next phase of the industrial revolution.<sup>1</sup> From better healthcare to safer transport and more sustainable farming, AI is bringing major benefits to our society and economy.<sup>2</sup> In the health sector, AI is being developed to manage clinical data or patients, to facilitate diagnostic and therapeutic decisions, to analyse medical imaging, laboratory and genetic data, to support patients with chronic diseases, as well as drug development and clinical trials.<sup>3</sup> However, although useful e.g. for the analysis of imaging data, many of these applications are not yet ready for use in routine care.

AI is not only an innovation booster, its use also creates risks. In particular, a learning AI is some kind of black box into which data is fed and from which results are produced in a complex manner based on training data. Often it is impossible to determine why and how the AI system has arrived at a given result. If the AI system produces an erroneous result, which leads to inappropriate decisions, this can be significantly problematic for those involved.<sup>4</sup> Therefore, in April 2021, the European Union

published a proposal for an Artificial Intelligence Act (AI Act).<sup>5</sup>

## Comprehensive European-wide legal framework

The proposal lays down a uniform legal framework across the European Union for the development, marketing, and use of AI. It aims at providing a high level of protection of health, safety and fundamental rights, and at ensuring the free, cross-border movement of AI-based goods and services.<sup>5</sup> The proposed act is currently discussed by the co-legislators, the European Parliament, and the Council. In Council, negotiations to find a common position between EU Member states have started.<sup>6</sup> The regulation could take effect over a transitional period in the second half of 2022. During this period, standards would be mandated and developed, and the established governance structures would become operational. The second half of 2024 is the earliest time the regulation could become applicable to operators with the standards ready and the first conformity assessments performed.<sup>4</sup>

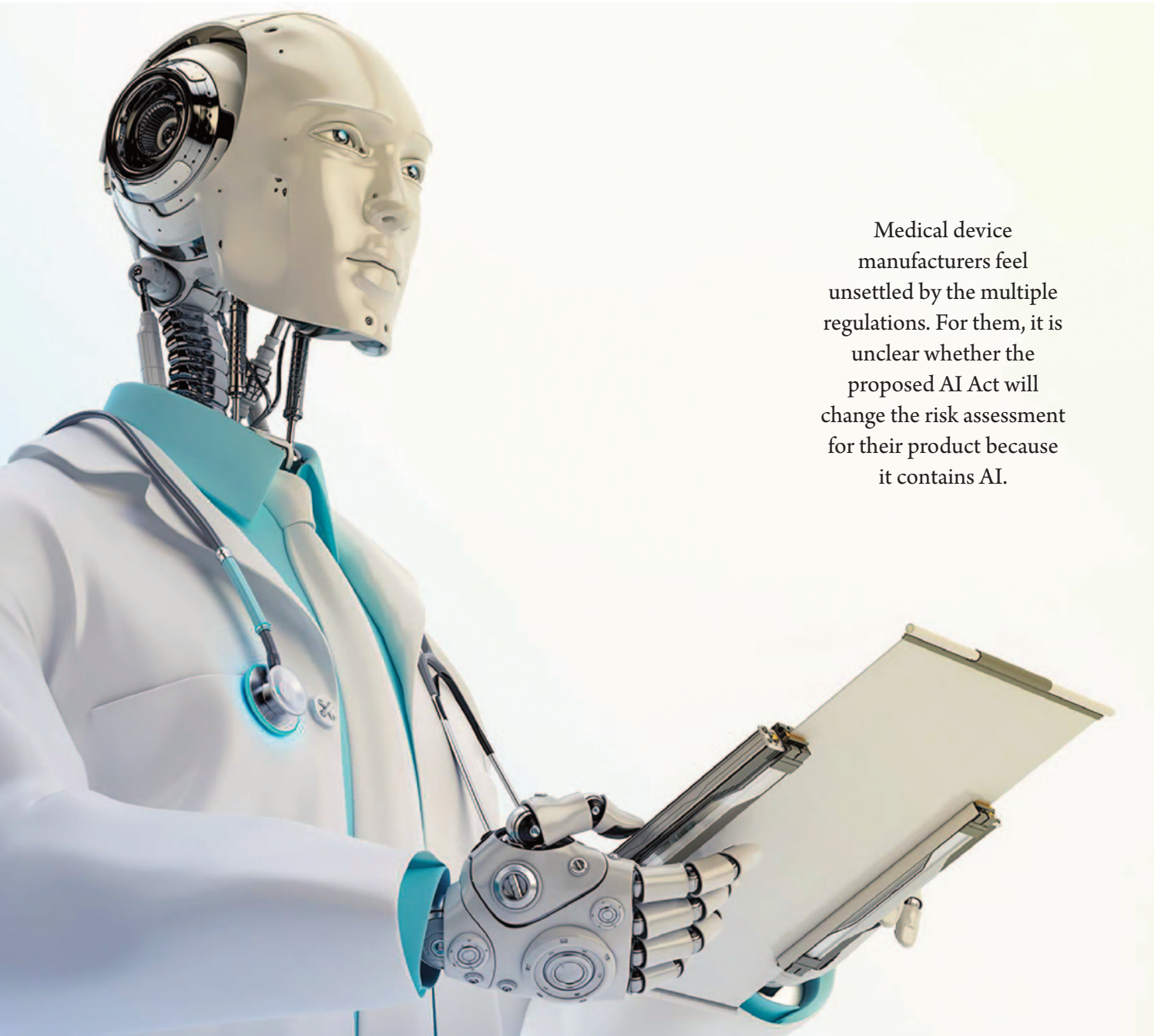
The proposal for a European AI Act considers some particularly harmful uses of AI as unacceptable, e.g. social scoring by governments, exploitation of children's vulnerabilities, and using subliminal techniques. The act will also subject live remote biometric identification systems in publicly accessible spaces used for law enforcement purposes to narrow exceptions (see Article 5 of AI Act proposal).<sup>5,7</sup>

## Focus on high-risk applications of AI

The proposed AI Act focuses on "high-risk" AI use cases. Whether an AI system is classified as high-risk depends on the intended purpose of the system, on the severity of possible harm, and the probability of its occurrence. High-risk AI systems falling under the proposal are systems used for biometric identification and categorisation of natural persons, for management and operation of critical infrastructure, for access control to education and vocational training, and for employment purposes, workers management, and access to self-employment. Further categories of high-risk AI systems described in Annex III of the AI Act proposal control access

to essential private and public services and benefits such as financial credit or medical aid. They are used for law enforcement purposes, for migration, asylum and border control management, and for the administration of justice and democratic processes.<sup>5</sup>

Additionally, and more relevant to AI-based medical devices and in vitro diagnostics, AI systems intended to be used as safety component of products and AI products falling within the scope of certain Union harmonisation legislation that are subject to third party ex-ante conformity assessment [i.e. by an external party before being



Medical device manufacturers feel unsettled by the multiple regulations. For them, it is unclear whether the proposed AI Act will change the risk assessment for their product because it contains AI.

placed on the market or put into service], are classified as high-risk (see Article 6 and recital 30 of AI Act proposal).<sup>5</sup> “Safety component” is defined as a component of a product or of a system which fulfils a safety function for that product or system or the failure or malfunctioning of which endangers the health and safety of persons or property (see Article 3 (14), AI Act proposal).<sup>5</sup>

#### **Unsettled medical technology manufacturers**

What does this mean for manufacturers of software-based medical devices? “Almost all

software used in medicine is subject to Class IIa or higher and thus must undergo a conformity assessment procedure before a notified body. Therefore, AI medical devices are almost invariably regarded as ‘high-risk devices’”, comments digital expert Natalie Gladkov of BVMed, the German Medical Technology Association that represents over 240 manufacturers, distributors, and suppliers in the medical technology industry. She considers this classification as too general and advises the application context should be considered more strongly, e.g. whether an AI medical device

merely supports medical staff or completely replaces them. “With the implementation of the MDR (Medical Device Regulation), CE-certified medical devices, such as algorithm-based solutions, already have a very high level of safety and quality for patients. Medical device manufacturers feel unsettled by the multiple regulations. For them, it is unclear whether the proposed AI Act will change the risk assessment for their product because it contains AI”, Ms Gladkov observes. (See explanation of software risk classes according to MDR-box).

**Explanatory box: Software risk classes according to MDR**

According to rule 11 of the MDR, software intended to provide information which is used to make decisions with diagnosis or therapeutic purposes is classified as class IIa. If such decisions have an impact that may cause death or an irreversible deterioration of a person's state of health, risk class III applies. If such decisions have an impact that cause a serious deterioration of a person's state of health or a surgical intervention, class IIb applies. Software intended to monitor physiological processes is classified as class IIa. However, if the software is intended for monitoring of vital physiological parameters, and variations of those parameters could result in immediate danger to the patient, it is classified as class IIb. All other software belongs to class I. For risk classes higher than class I, a notified body must be involved for conformity assessment.

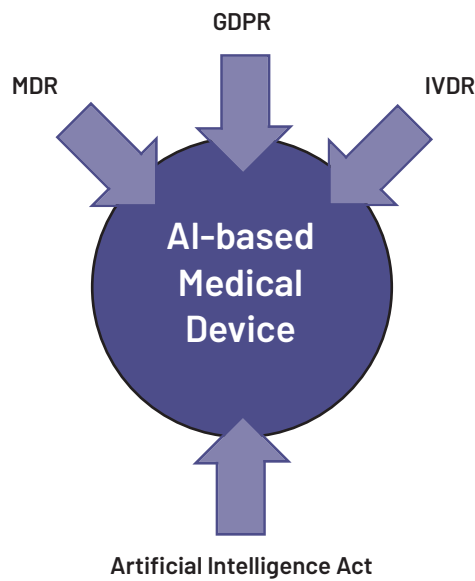
**Overregulating and superfluous?**

The EU AI Act proposal aims to define AI systems as technology-neutral and future-proof as possible.<sup>8</sup> To this end, the legislator defined an AI system as software that is developed with one or more of the following techniques: Machine learning approaches, logic- and knowledge-based approaches, statistical approaches, Bayesian estimation, and search and optimisation methods. It can, for a given set of human-defined objectives, generate outputs such as content, predictions, recommendations, or decisions influencing the environments they interact with.<sup>5</sup>

This definition classifies almost all existing and future software as AI, which may lead to overregulation, criticises Patrick Glauner, Professor for Artificial Intelligence at the Deggendorf Institute of Technology.<sup>1</sup> BVMed comments to prevent market access barriers for medical device manufacturers, a narrowing of the definition of AI systems is urgently needed.<sup>9</sup> Dr Glauner suggests that additional regulations should only address novel use cases that are not yet covered by existing regulations. He argues that the proposed regulation is not needed due to existing regulation and lacked delimitation from existing regulations (see also Figure 1).<sup>1</sup>

**Additional rules and draconian penalties**

The EU's AI Act proposal provides that high-risk AI systems need to respect a set of requirements



**Figure 1. Multiple regulations affect AI-based medical devices**

MDR and IVDR cover many but not all applications of AI in the healthcare sector, e.g. not an AI system to make and manage appointments. The intended purpose of an AI-based device determines which regulation applies.<sup>10</sup> The GDPR serves data protection purposes.

Abbreviations: MDR, Medical Device Regulation; GDPR, General Data Protection Regulation; IVDR, In vitro Diagnostics Regulation.

that include appropriate risk assessment, mitigation and control measures, and the use of high-quality data. Additionally, appropriate technical documentation and record-keeping, transparency and provision of information to the user, the design and implementation of appropriate human oversight measures, and high standards in terms of accuracy, robustness and cybersecurity, have to be considered.<sup>4,5</sup>

Once the AI system is on the market, authorities will be responsible for market surveillance, users shall ensure human oversight and monitoring, and providers shall have a post-market monitoring system in place. Providers and users shall report serious incidents and malfunctioning. If substantial changes happen during the AI system's lifecycle, the

system needs to undergo conformity assessment again and comply with AI requirements (see AI Act proposal, Article 43 para. 4).<sup>4,5</sup> Non-compliance with the proposed AI Act carries a penalty of fines up to €30 million, although the proposal states that penalties should take into particular account the interests of small-scale providers and start-ups and their economic viability (see AI Act proposal, Article 71).<sup>5</sup>

**Further adjustments and clarification required**

AI expert Dr Glauner considers that the proposed requirements for the development or use of AI in safety critical application areas are disproportionate and inhibit innovation for the healthcare sector – particularly those requirements outlined in Article 11 (Technical documentation), Article 60 (EU database for stand-alone high-risk AI systems), and Article 62 (Reporting of serious incidents and of malfunctioning) of the proposed AI Act.

Moreover, the requirements of the proposed AI Act regarding data sharing and documentation (outlined in Article 64 and Article 53) are unfeasible because of lacking infrastructure, intellectual property conflicts, and potential liability issues.

Dr Glauner fears that the regulation would make the use or development of AI applications in safety critical application areas such as healthcare almost impossible in the EU, further

strengthening the leadership of Chinese and US AI-services providers who also have the financial power to implement GDPR-compliant services and to weather fines and lengthy trials.<sup>1</sup>

**Doubled post-market surveillance**

AI-based medical devices are mostly software which, as part of a medical device, is covered by the CE marking of the overall device or, in the form of stand-alone software, is a medical device with its

**In view of the already very tight post-marketing control regarding health-related risks under the vigilance system of the MDR, an additional control and intervention possibility [...] regarding health-related risks on the basis of the EU AI Act seems superfluous and not justified.**

own CE marking. Article 65 of the EU AI Act proposal in conjunction with Article 67 para. 1 provides for additional regulatory post-market surveillance of medical devices by the market surveillance authorities competent under the MDR – with powers up to and including a recall request for products, for example, if the product presents a health risk, writes Ms Gladkov. The MDR already provides a differentiated system and specifies under which conditions manufacturers or the competent authorities must take corrective measures, if necessary withdrawals and recalls, in case of non-compliance [with the MDR] or health risks (confer Article 10 para. 12 MDR and Article 95 ff. MDR). Chapter VII of the MDR imposes comprehensive post-market surveillance and vigilance obligations on economic operators as well as close market surveillance by the competent authorities, explains the digital expert.<sup>9</sup>

In view of the already very tight post-marketing control regarding health-related risks under the vigilance system of the MDR, an additional control and intervention possibility [...] regarding health-related risks on the basis of the EU AI Act seems superfluous and not justified, criticises Ms Gladkov. “Extensive retesting of already CE-certified devices and the ambiguity that accompanies conflicting regulations must be avoided. This would delay access for all patients to highly innovative, affordable AI medical products in Germany and the EU”, she adds.<sup>9</sup>

#### Data protection and intellectual property issues

The AI Act proposal demands that training, validation and testing data sets for high-risk AI systems are relevant, representative, free of errors, and complete (see Article 10 para. 3). To achieve this, Ms Gladkov suggests that manufacturers be able to obtain access to comprehensive training data for their AI software to be able to develop AI solutions without bias, e.g. to statutory health insurance data administered by the currently established research data centre of the German Federal Institute for Drugs and Medical Devices. “So far, this is not possible”, the digital expert remarks. A standardisation of the legal framework would be required, e.g. regarding the EU AI Act, the General Data Protection Regulation (GDPR), and local data protection regulations for research. Moreover, BVMed recommends regulating only basic safety and performance requirements in the EU AI Act

to avoid a standards jungle that would make the observance of the “generally acknowledged state of the art” (see Annex I Chapter I para. 1 MDR/In vitro Diagnostics Regulation (IVDR)) required of manufacturers very burdensome.<sup>9</sup>

BVMed also criticises the requirement of common technical documentation for high-risk AI under Article 11 para. 2 of the AI Act. This could complicate co-operations between companies and create intellectual property issues. AI manufacturers and medical device manufacturers may even have to merge two technical documentations. A clarification in Article 11 para. 2 that exceptions are possible if the manufacturer of the AI and the “related product” are not identical would be useful in this respect, declares BVMed.<sup>9</sup>

#### The question of liability in case of damage by AI

The AI Act proposal aims at preventing and mitigating safety risks caused by AI systems. An important question regarding self-learning AI systems concerns who is liable for damages caused by such systems. BVMed believes that a gradual adjustment to harmonise liability regulations may be necessary, since these systems change their performance independently during operation. For example, additional risks may arise from the fact that erroneous, incomplete, or discriminatory data from the relevant clinical areas are processed, causing a deterioration of the security and performance of the software.<sup>11</sup>

“Examples of the use of software from the areas of prevention, diagnosis, therapy, and medical research have shown that – unlike in the convenience or lifestyle sectors – AI systems in the medical field do not usually act fully autonomously, but are supervised by doctors or researchers. The solutions to date function as a support for qualified personnel and do not replace them”, states BVMed law expert Katja Marx. “Furthermore, even an autonomously acting system can be assigned to the area of responsibility of a manufacturer or an operator. This is because even the more or less large degree of autonomy is based on certain designs and programming of the software by the manufacturer. The operation as well as updates or the plausibility check of results, e.g. by a physician, can always be attributed to a

responsible person that is liable in case of damage”, she explains.

#### Notified bodies are preparing for the coming AI framework

Dr Abtin Rad of the German Notified Body TÜV SÜD Product Service GmbH comments that there are currently not many industry-specific guidelines and standards on how to achieve conformity with the requirements of the MDR and the AI Act for medical devices. “In any case, there is a need for action here so that

manufacturers do not find themselves in the difficult situation of having to identify the state of the art for proving conformity themselves. Additionally, designation of notified bodies is an aspect that still needs to be specified in detail”, he adds. TÜV SÜD has established a team of experts and a task force to track and assess the current requirements from the draft AI regulation and how these would then be implemented for customer’s Quality Management System and products. “We also consider how to implement the

Medical device manufacturers will face additional vigilance requirements, such as for incidents not covered by the MDR and an expansion of the technical documentation for AI.

authorisation requirements for conducting the AI conformity assessment, as well as the processes and work instructions for the AI product assessment”, Dr Rad explains. Medical device manufacturers will face additional vigilance requirements, such as for incidents not covered by the MDR and an expansion of the technical documentation for AI.

Regulatory experts recommend awaiting and considering the International Medical Device Regulators Forum’s (IMDRF) harmonised approach to regulating AI-enabled medical devices. The EU should also be aware of the international competition in the field of AI by Asian countries and North America. In recent years these countries have propelled strategies for the development and strengthening of AI, as well as its regulation and standardisation often more effectively than has the EU.<sup>12</sup>

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

## Disclosures and conflicts of interest

The author declares no conflicts of interest.

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**Don't miss!**

## The September 2022 edition



### **A virtual workforce**

Working remotely/working from home has become the norm these days. This issue will focus on various aspects of working from home – the good, the bad, the ugly. We will have articles on the challenges of writing from home, managing teams and also, on how some of us overcome these challenges and enjoy this opportunity.

**Guest Editors: Archana Nagarajan**

# How the EU Medical Device Regulation is affecting the medical device landscape

An interview with Suzanne Halliday,  
the Regulatory Head of BSI, Medical Devices Notified Body

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## Abstract

Suzanne Halliday, D.Phil., is the Vice President for Regulatory within the Notified Body BSI with extensive experience in compliance to the Medical Devices Directive (MDD), ISO 13485, risk management, clinical evaluations and investigations, meeting essential requirements with harmonised standards, post market surveillance, and vigilance. She has a Bachelor's and Master's in Science (University of Waterloo) and a Doctorate in Engineering (University of Oxford). Prior to working for BSI, she has designed orthopaedic implants and conducted post market clinical investigations on these products.

The EU Medical Device Regulation (MDR) has drastically changed the regulatory environment for medical devices and reinforced the requirements on clinical evidence and the post-market surveillance. We are glad to have interviewed Suzanne Halliday for this issue of MEW with special focus on medical devices.

**Medical Writing (MEW):** The EU Medical Device Regulation (MDR) entered into force on May 25, 2017, and it has applied since May 26, 2021. What are your impressions as a Notified Body (NB) now 1 year after implementation?

**Dr Halliday (DH):** BSI has issued our first few hundred MDR and IVDR (In-vitro Diagnostic Device Regulation) certificates. Our teams of quality management system (QMS), microbiology and technical specialists have now implemented the processes that were developed for designation. After actually assessing conformity to the Regulations, people have gained confidence in their abilities and manufacturers' applications have started to flow more smoothly.

**MEW:** Could you please explain what you mean by "...have now implemented the processes that were developed for designation".

**DH:** When the NBs applied to be designated to the new EU Regulations, the applications consisted of process flow diagrams and procedures and forms and templates; however none of these had actually been used to assess conformity of any medical device. None of the NBs were allowed to take on any actual conformity assessment work until they were designated. What has happened recently is that technical specialists and QMS teams have used the documents in combination with their expertise. Nothing was perfect when it was based on theory and so our processes, procedures, forms and IT systems now are improving based on hundreds of people completing hundreds of reviews.

**MEW:** What were the biggest challenges that you experienced as a NB to ensure BSI was MDR ready?

**DH:** BSI was the first NB to be designated to the MDR and the second to be designated to IVDR. The Regulations are more prescriptive; however, BSI was already doing many of the activities required by Annex VII. The greatest challenges remain how to interact with EUDAMED (European Database for Medical Devices) and trying to keep up with training our teams on the thousands of pages of MDCG (Medical Device Coordination Group) guidance that have been developed.

**MEW:** How do you foresee the MDR changing the medical device landscape? Do you expect any negative effect on the availability of legacy and niche products or the development of new devices?

**DH:** Many articles have been written about the increased requirements for clinical evidence.

If manufacturers were writing their clinical evaluation reports in line with MedDev 2.7.1 Rev 4 (2016), there are only a few additional requirements to reach the requirements of the EU MDR.

The regulation has a prescriptive frequency of update for new documents including periodic safety update reports (PSUR) and summary of safety and clinical performance (SSCP). The regulation also has a prescriptive sample size and frequency of technical documentation reviews. These increased numbers of reviews will increase costs to

Nothing was perfect when it was based on theory and so our processes, procedures, forms and IT systems now are improving based on hundreds of people completing hundreds of reviews.





manufacturers. Unfortunately, this may result in some manufacturers choosing not to place a product on the market in the EU.

**MEW:** Are you able to estimate the increased effort required for submissions for CE marking under MDR compared to MDD /AIMDD (Active Implantable Medical Device Directive), both from a manufacturer's point of view and from a NB's perspective?

**DH:** Conformity assessment from the NB must be considered an initial assessment for devices to be listed on MDR certificates. This is true even of safe devices that have evidence of performing as intended for 10, 20, and 30 years. The initial assessment is taking time that used to be spread over many years in the past.

**MEW:** Could you please elaborate on this?

**DH:** When there were legislation changes in the EU in the past there were a few extra new things to check. The M5 amendment (Directive 2007/47/EC) moved Essential Requirement (ER) #14 to ER#6a, which means that a clinical evaluation was required for all devices. This amending regulation also required the review of specific risks of single use devices, specific justifications for clinical investigations not being performed for high risk devices and specific justifications for not completing post-market clinical follow-up (PMCF); however we did not re-review all of the technical documentation. The EU Regulations require all technical documentation to be re-reviewed.

**MEW:** What are some of the most common problems for manufacturers that you have seen as a NB with the transition to the MDR?

**DH:** There is an acute lack of resources in the competent authorities who complete reviews of ancillary medicinal substances. MDCG 2020-12 requires that these are initial assessments (which can take 210 days to complete), despite the pharmaceutical legislation not changing. Time is running out for manufacturers to make these submissions and have them completed by May 2024.

**MEW:** "Sufficient" clinical evidence seems to be the main topic for clinical evaluators under the MDR. What is your interpretation of "sufficient" for different risk classes of devices?

**DH:** EU Directives clarified the requirements for PMCF on the actual devices covered by CE certificates if those devices were placed on the market based on equivalence to another device. These clarifications were published in 2007 and should have been fully implemented by 2010. That should mean that actual data have been collected for more than 10 years. That could be "sufficient" to meet initial MDR requirements and then build on that manufacturer's evidence for all subsequent changes.

**MEW:** As a follow up to the previous question, there seems to be more value placed on small investigator-initiated studies that gather patient-reported outcomes over survival data from national registries; what hierarchy of evidence do you follow? How would you suggest addressing the challenges of obtaining sufficient clinical evidence for low volume and short life expectancy products where it is not feasible to obtain data on a sufficiently powered sample of patients?

**DH:** There are strengths and weaknesses from information learned in proactive study collection and strengths and weaknesses from information learned in registry data. The NB consider all sources of information. PMCF study data can ensure that data are gathered on subpopulations, extreme sizes of devices or rare severities of disease. Registry data can ensure that data are gathered from many different sites, many different medical

professionals, and across the most and least compliant patients. We would encourage a mixture of data to meet the “sufficient” expectation.

**MEW:** What MDCG guidances can be expected in the future? When can we expect guidance on the PSUR and updated guidance to replace the MedDev 2.7/1 Rev 4 for clinical evaluations?

**DH:** The Commission has indicated that they will not replace all MedDev guidances that were generated for the Directives. They are trying to prioritise the guidances necessary to successfully implement the Regulations.

Each MDCG workgroup (WG) publishes a work programme. The 2022 programme for MDCG WG #3 Clinical does not include a replacement for MedDev 2.7.1. The 2022 programme for MDCG WG #4 PMS & Vigilance includes PSUR guidance, although no guidance for the NBs to complete their review of the PSUR. Unfortunately, despite the NB working on these requirements for more than 1 year, this will be developed separately by MDCG WG#1 NBO (notified bodies oversight).

**MEW:** Have you witnessed increased demand and new opportunities for medical writers under the MDR, and are there opportunities for medical writers to work for NB?

**DH:** BSI are seeing manufacturers hire temporary employees to support the peak in workload required by initial EU Regulation submissions.

**MEW:** How have manufacturers demonstrated sufficient training and professional experience required for clinical evaluators in the broad areas of clinical research methodology, information management, regulatory requirements, medical writing, and the device technology and application as defined in MedDev 2.7/1 Rev 4? How would you advise medical writers to gain sufficient training and experience to prepare a clinical evaluation?

**DH:** BSI try to contribute to the whole system by delivering our own webinars and roadshow presentations. We also try to deliver other presentations at Regulatory Affairs Professionals Society (RAPS), The Organisation for Professionals in Regulatory Affairs (TOPRA), Association of British HealthTech Industries (ABHI), the British In Vitro Diagnostic Association (BIVDA), etc., where there is wide attendance from manufacturers, consultancy firms, and other service providers to the manufacturers trying to place product on the market.

**MEW:** Could you please elaborate on this? Do the clinical evaluators in general have the required expertise or are deficiencies regarding the qualification frequent? What kind of expertise would you see crucial? Is there an optimal way to get prepared for this task?

**DH:** MDCG 2020 6 indicates that MedDev 2.7.1 Rev 4 is still applicable for review of devices under the MDR with respect to who should perform the clinical evaluation.

MedDev 2.7.1 Rev 4 indicates:

- The clinical evaluation should be conducted by a suitably qualified individual or a team.
- As a general principle, the evaluators should possess knowledge of research methodology (including clinical investigation design and biostatistics); information management (e.g. scientific background or librarianship qualification; experience with relevant databases such as Embase and Medline); regulatory requirements; and medical writing (e.g. post-graduate experience in a relevant science or in medicine; training and experience in medical writing, systematic review, and clinical data appraisal).
- There are also requirements for specific knowledge of the device technology, diagnosis and management of the conditions intended to be managed by the device, and medical alternatives to the device under review.

Our Clinical Masterclass webinar series provides lots of additional information.

<https://www.bsigroup.com/en-IN/medical-devices/resources/webinars/2022/mdr/clinical-masterclass/>

### Disclaimers

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

### Disclosures and conflicts of interest

The authors are employed by the medical device industry. The interviewee is employed by a NB.

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Don't miss!

## The December 2022 edition



## Open science and open pharma

Open access ensures that the highest quality, peer-reviewed evidence is available to anyone who needs it, anywhere in the world. This issue will focus on how open access and plain language summaries improve transparency, advance medical science and ultimately improve patient care. Focus will also be given to how Open Pharma, a group of pharmaceutical companies and other research funders, alongside healthcare professionals, regulators, patients, publishers and other stakeholders in healthcare, are driving this goal.

**Guest Editors: Martin Delahunty, Tanya Stezhka,  
and Chris Winchester**

# Optimizing the value of regulatory medical writers

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## Abstract

An expanding need for clinical documentation and regulatory health authority interactions during drug development has drawn increased attention to the role of the regulatory medical writer. This role is frequently misunderstood and poorly recognized. The American Medical Writers Association (AMWA) formed a working group in 2020 dedicated to defining the value that regulatory medical writers contribute. The purpose of this article is to demonstrate the value that regulatory medical writers bring to the drug development and approval processes and to explore the ways in which efficiencies in regulatory writing can be increased. Current models for success provide guidance on training to help medical writers achieve their full potential, but obstacles and barriers to medical writing efficiency and document quality remain. Surveys developed by the AMWA working group revealed that (1) regulators who review clinical documents believed that regulatory writers improve document quality and (2) writers are frequently recognized for leadership and collaboration. Maximizing medical writing value requires thoughtful leadership and investment in training that includes both technical knowledge and soft-skill proficiency.

## Introduction

Expansion of the biopharmaceutical industry has given rise to many jobs with very specialized skills sets supporting both the conducting and reporting of clinical trials. One of these specialized jobs is that of the medical writer. There are now several types of medical writers: those who focus on clinical data publication writing, those who support medical education and conference materials, and those who primarily prepare regulatory documentation supporting ongoing clinical trials (eg, clinical study protocols, investigator brochures, investigational new drug [IND] applications) and the reporting and submission of trial results to regulatory agencies (eg, clinical study reports and Module 2 clinical summary documents for marketing applications). Writers in this latter category have been termed “clinical writers,” “regulatory writers,” or “clinical–regulatory writers,” and exploration of the value of their role is the focus of this article. For purposes of the current discussion, these writers will be referred to as regulatory writers.

Companies engaged in the development of new medicines have a high need for expert communicators and devote substantial budgets to ensuring that documentation supporting clinical trials and regulatory submissions is accurate and of high quality. However, because company structures and team structures vary significantly, expectations of the role of the regulatory writer may also vary. Full exploitation and harnessing of the writer’s skills and value requires members of the clinical project team to have a common understanding of the writer’s role. As this proposition regarding the value of the regulatory writer has become a prominent topic in the medical writing community, the American Medical Writers Association (AMWA) has formed a working group focused on understanding and communicating the value that regulatory writers bring to project teams. The remit of this working group included developing a series of surveys designed to gather information about the value that regulatory writers represent, as well as a thorough review of the literature to identify articles that address this topic. This article aims to demonstrate the value that regulatory writers bring to the drug development and approval process and to explore both common obstacles to efficiency and ways we can increase efficiencies in regulatory writing,

including through improved training of medical writers industry wide.

## Current models for success

A Medical Writing Competency Model was developed by an industry-wide group of medical writers to provide guidance on how to assure quality and consistency in the medical writing function.<sup>1,2</sup> It also serves as a tool to describe the value and contributions of medical writers to drug development and medical communications. The model defines the essential knowledge, skills, abilities, and behaviors (KSABs) necessary for medical writing competency. It is purposefully designed to include the scope and breadth of the medical writing profession, and it is applicable to both medical writers and managers of medical writers.<sup>1</sup> The Competency Model establishes 5 core competency domains through which the KSABs applicable to medical writing can be assessed and a medical writer’s competency can thus be certified.<sup>1,3</sup> These 5 core competency domains are gathering, evaluating, organizing, interpreting, and presenting.<sup>3</sup> They are the backbone of medical writing certification and the foundation of the Medical Writer Certified (MWC) examination.<sup>1,4</sup> In addition to defining and facilitating assessment of the core competencies that contribute to a medical writer’s value, the Medical Writing Competency Model and MWC examination inherently provide guidance on training to help medical writers achieve their full potential.

## Obstacles to efficiency

Notwithstanding the training and competency models currently available, there are still substantial obstacles and barriers to efficient medical writing to be recognized, acknowledged, and overcome. These obstacles have a significant and direct impact on submission timelines, success, and ultimately the speed of delivery of new medicines to patients.

## Lack of adequate writing skills and strategy

Documents prepared without using lean writing techniques take longer to write, review, approve, and therefore submit. They also slow down the regulatory review and approval by agencies. Thus, not only the sponsors but also, ultimately, the end users of new drug treatments are affected by these documents that hinder readability and comprehension.<sup>5</sup>

Oshiro et al surveyed registrants of 12 non compulsory workshops on scientific publishing, in which respondents were asked what they found most difficult about preparing a manuscript.<sup>6</sup> Two of the most common barriers to manuscript publishing included uncertainty about how to organize. Lean writing techniques and technical skill in writing help give a writer clarity in structuring thought and organizing it into a meaningful order with a good thought flow. When a document is structured to present data in a manner that builds ideas, the reader can more easily follow what the intended messages are and can more readily understand the conclusions.

#### Insufficient time

A key barrier to efficient medical writing is having sufficient time to craft the documents. Writing is an iterative process and writing the scientific documents that medical writers prepare is also a collaborative process involving multiple stakeholders, all of whom bring different perspectives that are relevant to the totality of the storyline. This means that timelines for the writing activities need to allow for sufficient time to pull a large amount of information together from multiple sources and weave it into a cohesive document. Timelines need to permit teams the bandwidth to strategically review the ideas and data presented. Complex documents with many interrelated topics may require multiple reads, with adequate timelines supporting this activity.

In addition, the time available for medical writers to focus on the data presentations and honing of the messaging is often reduced because they are not given the right tools and processes to optimize their writing time. For example, in the absence of good templates, medical writers need to spend time on predefining headings, styles, and formats, which means that less time is available to spend on the scientific content.<sup>7</sup> They might be given PDF files as source documents, which means they must spend time reformatting content taken from these files; or the team might insist on not using a lean approach to presenting the data, and the medical writers are asked to produce long, unwieldy documents full of bulk. Because timelines are rarely extended to accommodate these extra activities, adequate checks for scientific rigor are foregone, errors may be overlooked, and the relevance of interrelated data points may not be captured.<sup>8</sup> As writers face ever-accelerated looming deadlines, they are working longer hours, resulting in increased errors and an overall loss of quality. A study on quality metrics for clinical study reports found that

for medical writers whose work rate exceeded the standard work rate by 1.5 times, it was more likely that major sections of the draft clinical study report required reworking than for medical writers whose work rate did not exceed the standard.<sup>9</sup>

#### Insufficient training

Good and continued training is crucial to ensuring that these regulatory documents are being written by medical writers who have the lean writing skills to present the data with a structure that improves readability and guarantees they are fit for purpose. Training is needed not only on communication of clinical messages but also in interpretation of the data in the first place. Sharma highlighted that the key barrier that medical writers from India face in producing quality regulatory documentation is training because of a lack of a standardized training curriculum.<sup>10</sup> Lack of training can result in flaws in connecting the results to the conclusions, leading to claims that are not adequately supported or are erroneously reported.<sup>8</sup> Diong et al conducted an analysis on research papers and found poor statistical reporting, including implied or gross spin, use of standard errors or the mean to calculate data variability, and lack of P value reporting for primary analyses.<sup>11</sup> This demonstrates a clear lack of understanding on how to be reporting this information, which could be avoided if medical writers had adequate training in this area.

#### Barriers to document quality

Given that regulatory documentation is critical for drug approval, these documents need to be of a high quality and accurately reflect the data supporting the proposed indication. Review of regulatory documents by subject matter experts during the authoring process ensures that the data have been correctly interpreted and that key messages are supported; however, getting reviewers to provide the necessary input can be challenging. As a result of competing priorities, they often do not have sufficient time for their review, which results in inadequate checks of methods, results, or conclusions and can contribute to the introduction or oversight of errors.<sup>8</sup>

Inconsistencies, both between documents in a submission dossier and between documents and their source data, hinder review by regulatory agencies, resulting in unnecessary questions and responses. Li et al provided an example of the review of an IND submission in which a discrepancy in a definition of a key term, which on the face of it may seem relatively minor, confused a regulatory reviewer who questioned the sponsor in the

regulatory response.<sup>12</sup> This error, which would have been simple to correct during document review or quality control, led to wasted time and effort on the sponsor's part and was a fully avoidable delay to approval.

#### Optimizing efficiency: Impacts of leadership and training strategy on medical writing value

Maximizing medical writing value requires investment in training and thoughtful leadership. How a medical writing department utilizes its writers may impact the value potential of the team. Managers who encourage specialization in a specific document type or phase of development (ie, the creation of functional silos) are working toward short-term efficiencies only. Functional silos can result in inefficiency and employee dissatisfaction.<sup>13</sup> Avoiding those silos is critical for establishing an environment of flexible and creative problem-solving, and writer overspecialization can lead to reduced knowledge, collaboration, creativity, and confidence.<sup>14</sup> This does not mean that medical writers should never work on the same document twice in a row. Indeed, a writer needs to write any one document type several times to become truly confident in the unique features of that document and understand its needs. But by allowing writers to work on multiple document types, in different therapeutic areas, they gain a broader understanding of how the documents relate to each other and how they need modifications for different settings. This broader oversight makes them better able to advise teams and construct documents that are more fit for purpose. Building an agile, broadly experienced team also positively impacts employee satisfaction and career development as it gives the writers more options to work in areas that better fit to their personal character (some writers enjoy writing about pharmacokinetics and others prefer safety topics), which keeps them engaged and gives them growth potential. Effective leadership thus requires investment in cross-training and broader development of writing staff; in other words, it requires seeking to create medical writing “generalists” rather than “specialists.” The value of generalists over specialists is known from other industries, and David Epstein, author of *Range: Why Generalists Triumph in a Specialized World*,<sup>15</sup> describes the benefit of more generalized training like this: “The more varied your training is, the better able you’ll be to apply your skills flexibly to situations you haven’t seen.”<sup>16</sup> This book describes many examples of the impact of broader education on the ability to solve problems creatively. The generalist trainee is not

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constrained to understanding the same repetitive pattern of working.<sup>15</sup> Likewise, a writer who has written for all phases of development and across a variety of regulatory and clinical document types will have a breadth of experience that lends itself to valuable and creative contributions to document strategy.

Beyond training at the document level, building a strong writing team requires leadership that combines informed hiring decisions with day-to-day demonstration of desired behaviors. When regulatory writers were surveyed, the skills they were most recognized for on their teams were leadership and collaboration skills (see *The Regulatory Writer's Perspective* on page 80), indicating that these soft skills are a critical dimension of the regulatory writer's role. The survey also revealed leadership skills, collaboration skills, and project management as the top areas in which writers desire more training. Managers need to hire staff with the curiosity and team spirit needed to form a solid working group. The managers themselves then need to lead by example of the desired traits that solidifies a team. This includes showing a willingness to ask the right questions and to collect varying viewpoints on a problem (Table 1). It also includes encouraging horizontal relationship-building with other functional areas so that the medical writing team has a shared vision and understanding of goals with those other functions.<sup>17</sup> Teammates who learn to collaborate across functional boundaries gain skills faster and increase business efficiencies.<sup>18</sup>

Multiple studies describe a link between employee satisfaction and effective training.<sup>19</sup> A study of human resource employees showed a statistically significant impact of training and development on employee satisfaction and concluded with a recommendation to provide training oriented not only to work tasks but also to the developmental goals of the employee (eg, more generalized training opportunities).<sup>20</sup> Not only do generalist skills aid writers' development, but these skills can also help them to progress in their career. The progression from individual contributors to managers to enterprise-level leaders requires multiple "seismic shifts" in thinking, including a willingness to train as a generalist as opposed to a specialist.<sup>21</sup> Supporting this idea, a survey conducted in 2013 revealed that 60% of respondents felt their manager was a "good generalist" with broad transferable skills in people management and leadership, which are necessary for more senior positions in an organization.<sup>22</sup> Broad training strategies, then, need a company's attention for both improving problem-solving as well as positively impacting employee

satisfaction and development into more senior roles, all of which elevate the value of the medical writing organization.

### Soft skills that increase efficiency and add value

Soft skills, in addition to technical knowledge, are essential for medical writing success.<sup>1,2</sup> These skills are increasingly recognized as an important contributor to competent job performance in a wide range of fields.<sup>1,2,23-36</sup> A recent survey was conducted with human resources and learning development specialists, including C-level executives, senior managers, and managers/supervisors, at companies ranging in size from <1,000 to >50,000 employees in a variety of industries, including technology, manufacturing financial services, health care, retail, hospitality, telecommunications, and education.<sup>36</sup> The survey found that across industries, the need for soft skills is nearly as difficult to fill as the need for hard skills.<sup>36</sup> The most in-demand soft skills identified by survey participants were critical thinking, communication, and creativity.<sup>36</sup>

However, as the need for soft skills grows, they are only briefly mentioned within the context of medical writing.<sup>1</sup> The Medical Writing Competency Model includes a list of soft skills in a supplementary table of general abilities that are applicable to all medical writers, regardless of their area of specialty.<sup>37</sup> These soft skills include assertiveness, compromise, decisiveness, kindness, conflict resolution, flexibility, leadership, resilience, negotiation, and openness.<sup>37</sup> Many of the soft skills listed in the Competency Model are mentioned in other articles on medical writers and medical writing.<sup>1,2,23-35</sup> Many of these authors identify additional soft skills they believe are also crucial for medical writer and manager competency (Table 2).

Many of these soft skills are relevant to the competency, and ultimately to the value, of all medical writers. An analysis of regulatory medical writing job opportunities posted on the European Medical Writers Association website between 2009 and 2011 ranked the behavioral and social soft skills required of medical writers by the frequency of their appearance in job posting advertisements (Table 3).

Medical writers are recognized by drug development stakeholders, including study sponsors and government agencies, as valuable contributors to drug research and regulatory processes.<sup>32</sup> Part of that value lies in their technical understanding of how to craft thought and their regulatory understanding of the needs of the various documents. Yet their soft-skill competency is an equally important aspect of their value for their ability to pull teams

together and keep stakeholders focused on messaging, timelines, and collaborative work ethics. Their ability to manage projects brings an essential value to their role. As noted by Ohms, a good project manager shepherds their projects and understands the interplay of the different functional areas involved.<sup>38</sup> Ohms points out that the 4 features of an exceptional project manager are

1. Respecting others earnestly,
2. Knowing when to speak and let others speak,
3. Understanding the details driving the project, and
4. Taking the time to self-assess and maintain focus. All of these features typify the skills that a good medical writer needs to have to successfully complete their projects on time and with a well written document.

### Feedback from regulatory agencies on the value of medical writers

The AMWA working group's survey designed for regulators who review documentation prepared by medical writers gave some valuable insights into how the agencies perceive the role of medical writers and the value they bring to regulatory documents (see *The Regulator's Perspective* on page 72). Regulators recognized and acknowledged the value that medical writers add to the regulatory documents they work on. They believe that medical writers improve document quality, which, unsurprisingly, is extremely important for regulatory reviewers. They confirmed that poor document quality can hamper the ability of the reviewer to provide an assessment, which in turn delays the drug approval process and in some cases can even sensitize reviewers to subsequent submission documents from the same sponsor.

These survey results provide meaningful data to support how we present ourselves within our organizations and how we should develop our medical writers – quality is clearly highly valued by regulators, and the regulators' feedback illustrates the need for a sufficient supply of highly trained writers. Ultimately, the regulatory reviewers made it clear that they are looking for lean but fully developed documents that make the scientific rationale clear and show how it is supported by the data. When training medical writers, we must equip them to lead teams to create documents that are concise and clearly present the message. There is also a clear need to focus on team management and soft skills that enable writers to lead and guide the authoring teams.

We can conclude that many regulatory reviewers understand the role of medical writers and

**Table 1. How to ask good questions**

Common Pitfalls	Effective Inquiry
Start with yes-or-no questions.	Start with open-ended questions that minimize preconceptions. (“How are things going on your end?”; “What does your group see as the key opportunity in this space?”)
Continue asking overly general questions (“what’s on your mind?”) that may invite long off-point responses.	As collaborations develop, ask questions that focus on specific issues but allow people plenty of room to elaborate. (“What do you know about x?”; “Can you explain how that works?”)
Assume that you’ve grasped what speakers intended.	Check your understanding by summarizing what you’re hearing and asking explicitly for corrections or missing elements. (“Does that sound right – am I missing anything?”; “Can you help me fill in the gaps?”)
Assume the collaboration process will take care of itself.	Periodically take time to inquire into others’ experiences of the process or relationship. (“How do you think the project is going?”; “What could we do to work together more effectively?”)

Adapted from Edmonson et al.<sup>18</sup>

believe that they make the job of the reviewer easier. Medical writers are clearly valued and respected by regulatory agencies, and these take-home messages should empower the medical writing profession and help to shape the ongoing training of medical writers.

**Optimizing the role of the medical writer**

To optimize the role a medical writer plays on cross-functional teams, we need to understand the skill set that these writers require to play this role well. Ultimately, a good medical writer must master 3 main areas: writing skills, understanding the regulatory needs of the documents they are writing, and inter-personal skills to effectively manage projects.

Writers need to have excellent writing skills to effectively communicate the thoughts and vision of the document from their teams. This involves not only knowing how to structure thought in well-formed sentences but also how to structure the document in such a way that a reader comprehends how the various data points build on each other to form the intended messages. Developing a good medical writer, therefore, must begin by having someone who already has a talent and passion for writing and then must progress to guiding them to hone their craft. Like any talent, writing skills get better with training. Teaching a writer to write better

requires having someone who already has the skills to take the time to review and revise the text of the learning writer to show them how to improve. This is an investment of more than just giving them a well-written document and asking them to emulate it. It needs a trainer who will pull apart what the writer wrote, reconstruct it, and then take the time to explain why and how. People learn by making mistakes, and it is only when we are shown those

mis-takes and understand how to avoid them that the learning process takes place.

Writers also need to understand the unique purpose of each type of regulatory document. Many of these documents contain similar information, but the intention of each document differs. Some are meant to communicate to investigators, others are meant to communicate to regulatory reviewers, and all of them need to tell a slightly different part of the story for different purposes. Medical writers not only need to learn the theory of the regulatory requirements specified by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and other agency guidelines that define what each document is meant to do but also need to be given sufficient guided practical training to see how teams build, discuss, and craft these documents.

This includes having the opportunity to see feedback from agency reviewers on different types of documents and be part of teams who revise the documents in response to this feedback. Think of the difference between learning to fly a plane by reading the instruction manual and spending 10,000 hours in the air with a coach. Only the latter produces a seasoned pilot. This is an instance in which the concept of a generalist compared with a specialist becomes salient. Ensuring that a writer has practical experience on a broad spectrum of documents across a clinical development program gives them more depth of knowledge and makes them more versatile overall. It means they can truly advise teams on what fit for purpose looks like for different document types and that they help teams

**Table 2. Important soft skill-based competencies not listed in the medical writing competency Model<sup>1</sup>**

Soft Skill	Cited in:
Project management	Pal 2019, <sup>24</sup> Limaye 2020, <sup>25</sup> Saleh 2020, <sup>27</sup> Guillemard 2014 <sup>28</sup>
Time management	Heisel-Stoehr and Schindler 2012, <sup>23</sup> Flaherty 2014, <sup>26</sup> Nice 2016 <sup>30</sup>
Multitasking	Heisel-Stoehr and Schindler 2012, <sup>23</sup> Pal 2019, <sup>24</sup> Nice 2016 <sup>30</sup>
Critical thinking	Flaherty 2014, <sup>26</sup> Guillemard 2014 <sup>28</sup>
Cultural competency	Heisel-Stoehr and Schindler 2012, <sup>23</sup> Flaherty 2014 <sup>26</sup>
Ability to work independently	Heisel-Stoehr and Schindler 2012, <sup>23</sup> Pal 2019 <sup>24</sup>
Work ethic	Heisel-Stoehr and Schindler 2012, <sup>23</sup> Flaherty 2014 <sup>26</sup>
Attention to detail	Heisel-Stoehr and Schindler 2012, <sup>23</sup> Nice 2016 <sup>30</sup>
Networking	Heisel-Stoehr and Schindler 2012 <sup>23</sup>
Self-motivation	Pal 2019 <sup>24</sup>

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**Table 3. Top-Ranked Soft Skills in EMWA Job Ads for Regulatory Medical Writers: 2009–2011<sup>23</sup>**

Behavioral Skills	Percentage of Ads	Social Skills	Percentage of Ads
Leadership, team working	62	Communication	47
Networking	56	Interpersonal	22
Organized	33	Work independently	18
Time management	30		
Detail-oriented	27		
Multitasking	15		
Conflict management	10		

Ads, advertisements; EMWA, European Medical Writers Association.

achieve that.

Finally, to optimize the value of a medical writer, we need to ensure that writers can train on the soft skills identified previously. This requires creating a safe environment that empowers them to challenge their boundaries as they learn how to assert themselves and corral teams. This training should come initially through demonstration, as novice writers witness experienced writers steering their teams and collaboratively working alongside other functional areas to develop documents. As writers develop, they must be granted increasing responsibility for running simpler meetings with an experienced writer there to support them, if needed. The acquisition of soft skills can be the most challenging dimension of writer development. Many writers are not extroverts by nature, and gaining the confidence to speak up and challenge subject matter experts often means overcoming their natural tendency to sit back and let others lead. By creating a situation in which writers first learn by example, writers are then allowed to execute within a safe environment and finally function independently once they have the necessary skills. We must give them the encouragement and security to grow without fear of embarrassment or risk of failure. In this way, we nurture strong, confident writers who have the wherewithal to collaborate with even the most demanding teams. Through training and development with a focus on both technical and soft skills and identification of growth opportunities for new and developing writers, we can continue to address the challenges discussed here and foster the next generation of regulatory writers.

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## New Special Interest Groups

Welcome to our new special interest groups!



# Value of medical writing: The regulator's perspective

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## Abstract

In 2020, the American Medical Writers Association established a working group to assess the value of the contribution of medical writers across the health sciences industry, including a subgroup tasked to gather data on the regulatory agency's perspective. We invited reviewers at regulatory agencies to participate in an anonymized survey to evaluate the effect of document quality on the regulatory review process, assess awareness among document reviewers of the contribution of medical writers to the quality of regulatory documents, and identify current strengths and opportunities to optimize document quality. This article shares the survey results and discusses their implications for document quality, their impact on the regulatory review process, and the skills medical writers need to develop to bring value to this process.

## Introduction

**M**edical writers bring value across the health sciences, taking the lead and driving efficient approaches for the delivery of high-quality medical communication documents targeted at diverse audiences including regulators, payors, physicians, and patients.<sup>1,2</sup> However, the value of medical writing is not consistently recognized, and medical writers often still need to justify why they should have a seat at the table and be part of the team earlier in the process. Medical writing departments can also be faced with insufficient budget and resource to do their best work due to a lack of understanding of the role's value. Given the many settings in which medical writers work and the variety of documents produced, it can be challenging to identify specific indicators of value. To address this issue, the American Medical Writers Association (AMWA) Executives Advisory Council established a taskforce to define and quantify the value of medical writing. The taskforce has 3 main areas of focus:

1. Perceptions of medical writer value among medical writers and their employers,
2. Key topics related to medical writer value, and
3. How the regulatory agencies view document quality and the value of medical writing.

This article presents the work of the regulatory agency sub-group to evaluate the effect of document quality on the regulatory review process and assess awareness among regulatory agency reviewers of the contribution of medical writers to the quality of regulatory documents. By understanding the regulator's perspective, we hoped to demonstrate how medical writers bring value to documents submitted to regulatory agencies, to identify and refine the training needs of medical writers, and to identify areas for action for the medical writing profession and for colleagues in the biopharmaceutical industry.

## Survey design and objectives

We employed an online survey format (SurveyMonkey), targeted at participants who were actively responsible for document review at a regulatory agency, were managers of regulatory agency reviewers, or who had worked in a regulatory agency review role in the past 6 months.

Participants were eligible regardless of the specific types of documents they reviewed. We identified potential participants via contacts in our own networks, via our colleagues (eg, company regulatory department), and via contacts of the AMWA Executives Advisory Council. Participants were also encouraged to forward the survey to other eligible individuals within their organization. We reached out to the United States Food and Drug Administration, Health Canada, the European Medicines Agency, the Medicines and Healthcare products Regulatory Agency, the Bundesinstitut für Arzneimittel und Medizinprodukte, the Pharmaceuticals and Medical Devices Agency, the National Medical Products Administration, and the Australian Therapeutic Goods Administration, although the agencies of those who actually participated are not identified, as the survey was anonymous. AMWA provided an official invitation letter and cover email to explain that the survey was being conducted on behalf of AMWA, its objective, and how the results will be used and to provide confirmation that the responses remain anonymous.

Being cognizant of limitations on the regulators' availability for such a survey, we made significant effort to develop a set of 25 survey questions that we believed would capture key points from the regulators' experience with document quality and medical writing. Most of the questions were multiple choice. The survey also included a checkpoint question to eliminate participants not involved in document review, and participants were invited to take part in a follow-up interview. For the follow-up interviews, we prepared 7 questions to elaborate on the survey results. For example, some questions included "none of the above" as a response option. If many participants selected this option, we requested additional information during the follow-up interviews.

After beta testing, the survey opened in April 2021 and was open through early August 2021. Interim views of the data were done in May/June to confirm adequate participation. Follow-up interviews were conducted during August 2021.

**Participant profile**

We received 32 responses to the survey. Although this was considerably higher than the anticipated response rate, the response rate was not uniform across all questions, and it was agreed that the sample size was appropriate for descriptive analysis only. In the following sections, we have highlighted where we believe the data should be interpreted with caution due to a lower response rate.

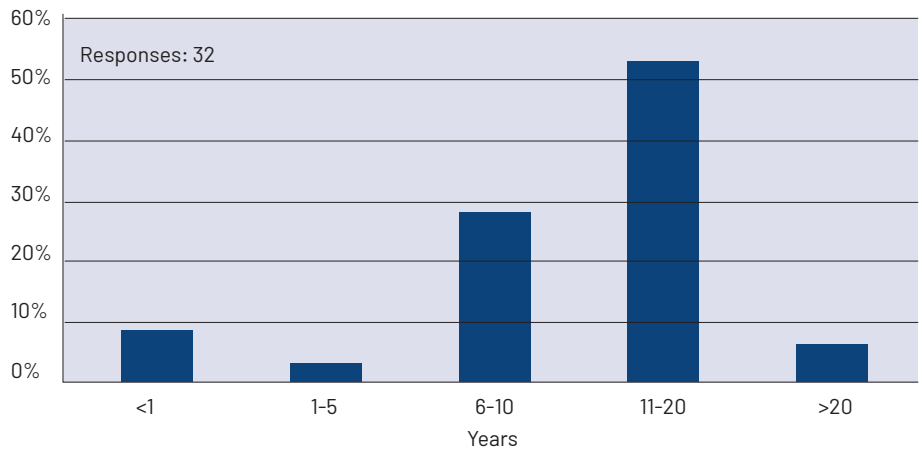
The data on agency tenure and time spent reviewing documents indicated that the survey was completed by participants meeting the target profile. Most had been employed at their current agency for over 5 years (Figure 1) and spent at least 10% of their time reviewing documents (Figure 2). Participants were also asked to indicate their department or division (omitting information that could identify them or their employer). Based on these responses, we were reasonably confident that we had engaged with the right people at the regulatory agencies for the purpose of this survey.

**Impact of quality on regulator assessments**

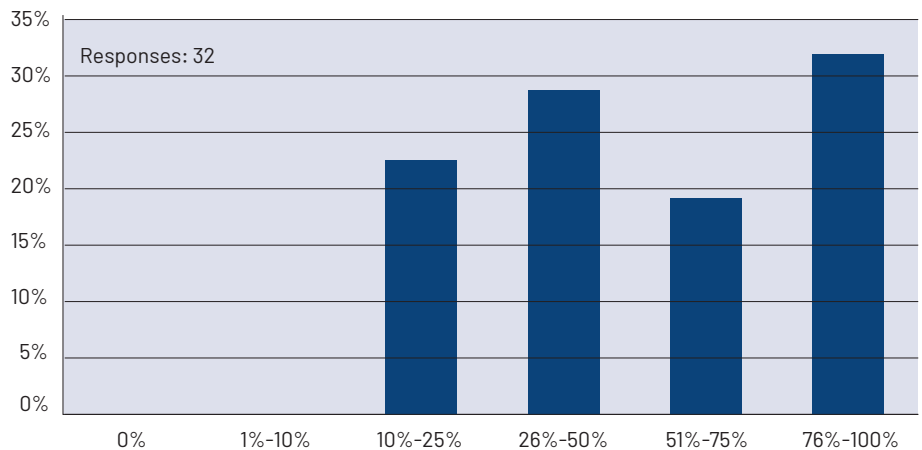
Medical writers will be familiar with how the work of internal and client teams is hindered when the documents they are given are poorly constructed. The survey results confirmed that the work of the regulatory reviewer is similarly impacted if documents submitted to the agency are not well written, and the responses provide important messages about the value of the medical writer. The following section also includes important information for colleagues in Regulatory Affairs or other functions involved in management of regulatory applications, as well as for corporate management.

The majority (87%) of the participants confirmed that poor document quality impedes regulatory assessment (Figure 3). Of note, none of the participants *disagreed* that poor quality impedes document review, and the remaining 13% had no opinion. When asked whether they encounter issues related to document quality during the review process, the same percentage – 87% – reported such issues either sometimes or often (Figure 4). These results show that regulatory assessors receive poor quality documents for their review relatively frequently, and regulatory assessment of the document is thereby impeded.

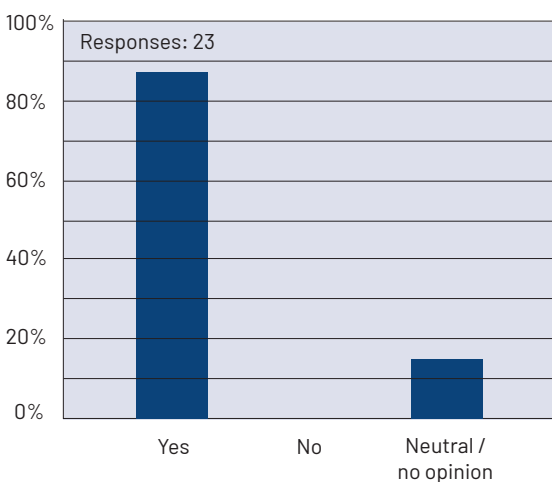
To gauge whether there has been any directional change in quality of documents, the



**Figure 1. How long have you been employed at your current agency?**

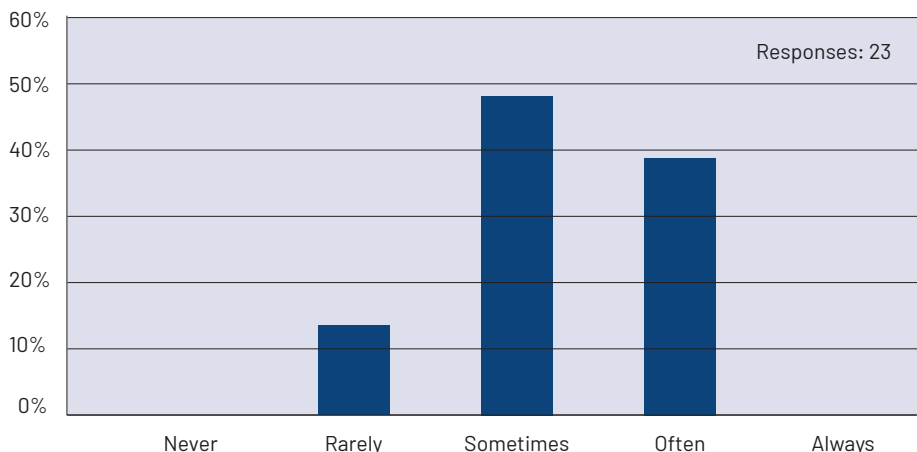


**Figure 2. In your current position/role, what percentage of your time do you spend reviewing documents**

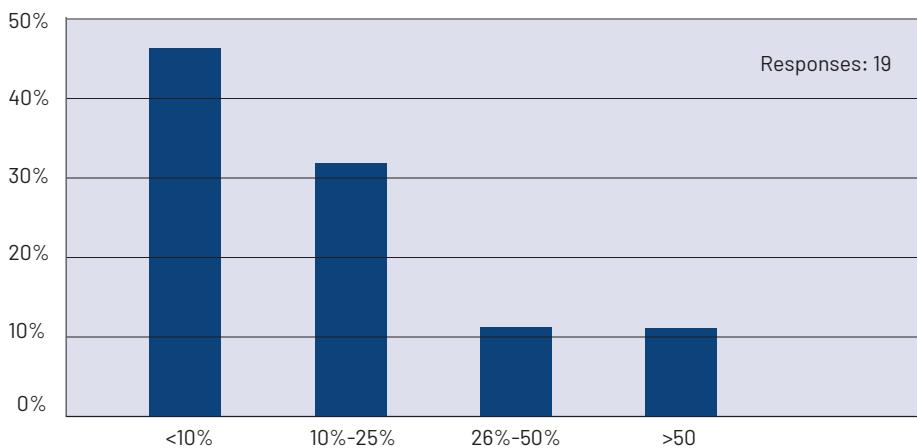


**Figure 3. Does poor document quality impede your ability to provide regulatory assessment?**

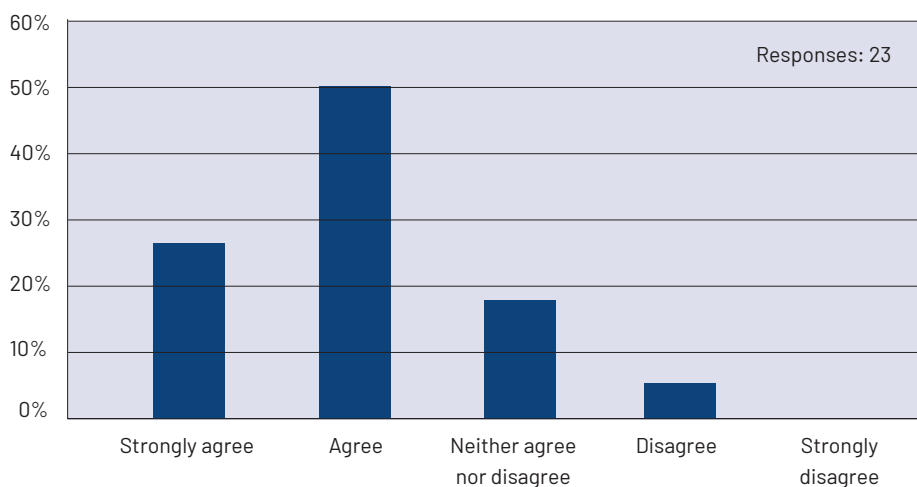
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**Figure 4. How often do you encounter issues related to document quality during the review process?**



**Figure 5. What percentage of applications do you reject/send back to the applicant with questions due to poor document quality?**



**Figure 6. For applications that are ultimately approved, a poorly written document delays the approval process.**

regulators were asked how document quality has changed in the past 5 years. Improvement in document quality was selected by 43% of participants. This indicates that the quality of submissions is moving in the right direction. However, there is still work to be done, because almost half (48%) responded that there has been no change in quality or they were neutral/had no opinion, and 9% believed that the quality of documents submitted to their agency has declined over the past 5 years. Note that at this point in the survey the participants had not yet been provided with examples of quality issues, and so these responses likely reflect the regulators’ own concept of document quality.

If documents within an application are of poor quality, the regulatory reviewer may need to send the application back with questions for clarification. Over half the participants (53%) said that they send over 10% of applications back or reject the application, with questions arising from poor document quality (Figure 5). Although 47% of participants send back or reject less than 10% of the applications, this still means that a sizeable number of applications are delayed. For applications that are ultimately approved (Figure 6), 77% of the regulatory reviewers agreed or strongly agreed that poor document quality will delay the approval process. These are clear messages on how poor document quality, which is an avoidable issue if proper processes are established and led by trained professionals, impacts the applicant’s goals and, perhaps of more serious consequence, leads to patients waiting longer than necessary for new medicines.

To understand whether poor quality might impact other documents in the regulatory assessment process, we asked whether a poorly written document negatively influences the review of other documents from the same applicant. Almost a third (27%) of participants agreed that poor document quality could negatively influence their review of the applicant’s other documents. It should be noted that we did not define what this means in practice, eg, whether the reviewer would be likely to review the applicant’s other documents in more detail or whether this approach would carry over to documents in later submissions. The same percentage (27%) disagreed with the question, and 45% neither agreed nor disagreed. This indicates that, in some cases, poor document quality can even influence the assessor’s review of the applicant’s other documents.

The survey included questions around whether the regulatory agencies collect data themselves on document quality. Three participants (13%) confirmed that their agency collects such data, 35% responded that these data are not collected, and 53% did not know. When asked what the agency does with the data, one participant stated the data are reviewed, but the majority skipped the question. Most participants (90%) responded that their agency does not keep a record of applicants that regularly submit poorly written documents.

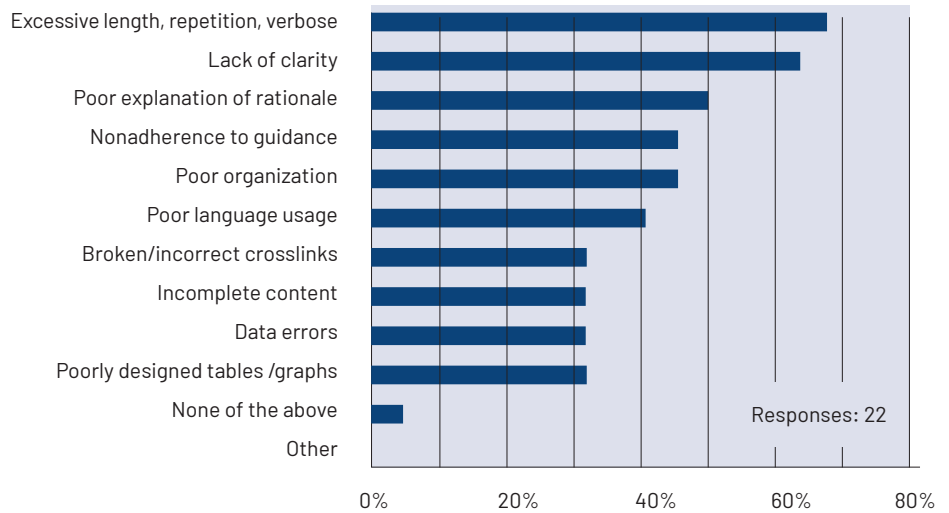
**Quality issues observed by the regulators**

Having established that document quality has a significant effect on the regulatory assessment process, it was important to understand which kinds of document quality issues are observed by the regulators. For the questions designed to identify these quality issues, participants were provided with the following response options (Figure 7).

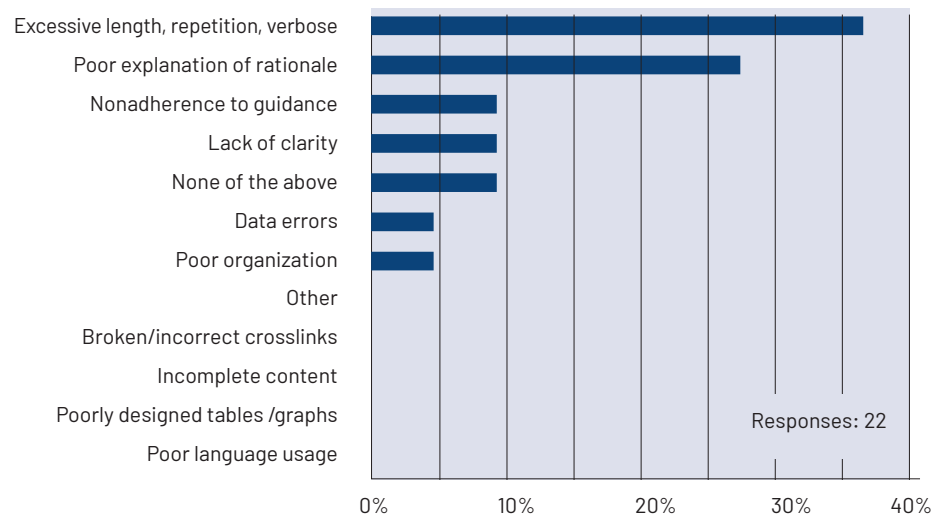
Poor organization
Poor language usage
Lack of clarity
Poorly designed/presented tables and graphs
Data errors (eg, inconsistencies, transcription errors)
Incomplete content
Poor explanation of rationale
Excessive length, unnecessary repetition, verbose
Incorrect format/nonadherence to guidance
Broken/incorrect or insufficient crosslinks
Other
None

**Figure 7. Examples of quality issues used in survey questions**

When asked to identify all quality issues encountered (Figure 8), those most frequently reported by the regulatory reviewers were excessive length/repetition/verbosity, closely followed by lack of clarity. This will not surprise most medical writers, who expend great effort working with teams to produce documents that are clear and concise with well-organized messages. However, these results do demonstrate that the effort invested in these aspects is warranted and necessary to meet the needs of the regulatory assessors. Of note, issues such as data errors, incomplete content, broken links, and



**Figure 8. Which of the following issues related to document quality do you typically encounter? Check all that apply.**



**Figure 9. Which one of these issues related to document quality do you encounter most frequently?**

poor tables/graphs were ranked relatively low in this question, which suggests many applicants have implemented processes to catch these avoidable issues prior to document submission.

In addition to the range of quality issues typically observed, we asked the regulatory reviewers to identify the one document quality issue they encountered most frequently (Figure 9). Excessive length/repetition/verbosity was ranked top here, too, closely followed by poor explanation of rationale. Once again, avoidable issues (data errors, incomplete content, poor tables/graphs, poor language) were ranked low or not at all.

Understanding the range and frequency of quality issues will help the medical writing profession and the industry to improve processes that support document quality and to target training and skills development for authoring teams. It is also important to understand whether specific quality issues have a greater effect on the assessor's review and application approval, regardless of how frequently they occur. Poor explanation of rationale caused the greatest negative effect on review or caused the most irritation to the regulatory reviewer, with excessive length ranked second (Figure 10). When asked to identify the one issue that has the

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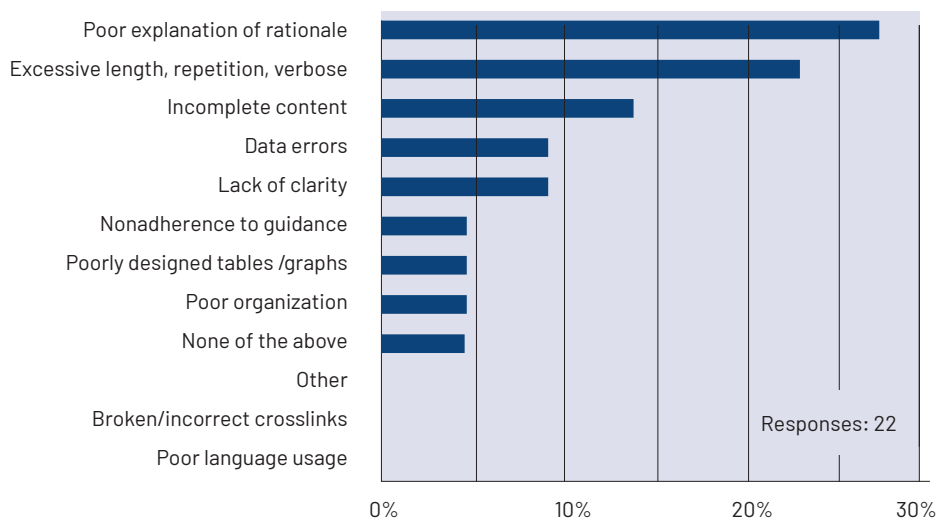


Figure 10. Which one of these issues related to document quality most negatively affects your review/causes the most irritation?

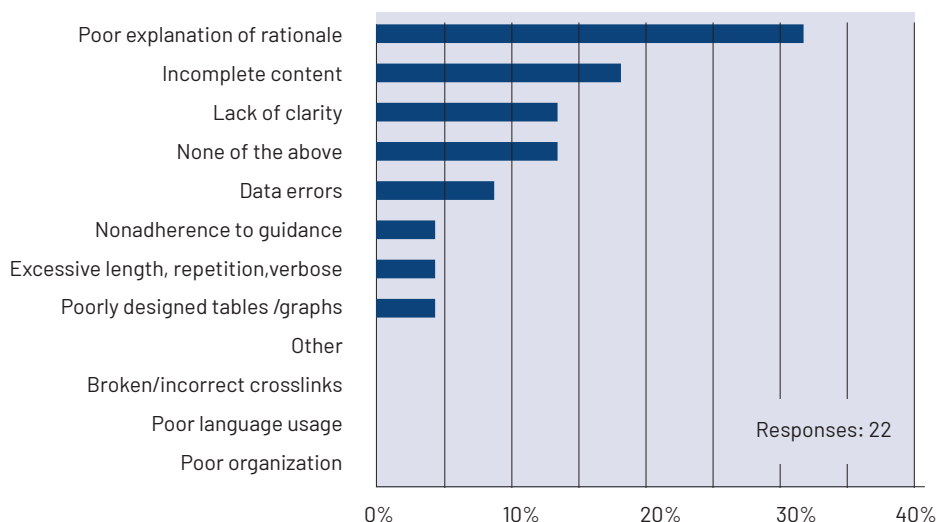


Figure 11. Which one of these issues related to document quality has the greatest negative effect on application approval?

greatest negative effect on application approval, the regulatory reviewers also ranked poor explanation of rationale at the top (Figure 11), followed by incomplete content. Poor explanation of rationale, therefore, is not only one of the most frequently observed quality issues, but also caused the most irritation to reviewers or negatively affected their review and has the greatest negative effect on approval. Clear strategic presentation of rationale supported by data should be a top area of focus for the teams responsible for documents

submitted to regulatory agencies.

It is also interesting that, although incomplete content is not among the most frequent quality issues, the responses suggest it has a large negative effect on application approval when it does occur. It is therefore important for applicants to have rigorous processes to validate documents for completeness before submission. In converse, excessive length was ranked as the most frequent and was among the top document quality issues that cause irritation or have a negative effect on regulatory review, yet it is not

among the top issues that negatively affect application approval.

Regulators’ perception of medical writing

Beyond their view of the documents themselves, we wanted to understand what the regulatory reviewers thought of medical writers, their role, and their effect on the documents sent to the regulators for review.

Of those who responded, 67% were familiar with the contribution of medical writers to the documents they review. Importantly, 70% either agreed or strongly agreed that medical writers improve the quality of these documents, and a clear majority (87%) agreed or strongly agreed that sponsor companies with established medical writing functions and rigorous document development processes and standards produce higher quality submissions. Although this last question was asked before we had given examples of quality (and so the regulatory reviewers have used their own idea of a high-quality document), the responses strongly indicate that medical writers improve quality and established medical writing functions and processes produce higher quality documents.

We asked the regulators to indicate any areas where they believed that medical writers add value to regulatory documents. Over 78% identified “adherence to standards,” and 71% identified “accuracy.” This was closely followed by 64% for each of the following:

- Clarity
- Completeness
- Explanation of rationale
- Formatting

It is particularly reassuring that the regulatory reviewers believe that medical writers add value in the areas of accuracy, adherence to standards, and also explanation of rationale, which the previous questions had clearly identified as a key area of concern for them. However, it should be noted that this question was only answered by 14 respondents, and so the results should be interpreted with caution.

Follow-up interviews

Some of the participants indicated that they would be happy to give more detail about their survey answers. We arranged individual interviews to gather this information, which was anonymized and amalgamated and is presented below.

### Quality issues and document type

Because the survey had identified quality issues in some of the documents that the regulatory reviewers receive, it was important to understand if these were most prevalent in one document type (suggesting an issue with the template or understanding of the requirements) or were seen in all of the document types received. The regulatory reviewers confirmed that quality issues were seen generally across all document types. They explained that templates or guidance cannot address all the nuances of writing these documents and so experienced writers are needed.

### "Explanation of Rationale" as the key quality issue

Explanation of rationale was identified as a key area of importance for the regulatory reviewers, and they explained that this was because it can take them a lot of time to interpret what the author intended to communicate. The reviewers often go back to the sponsor for clarification, but this depends on several factors:

- The type of document being reviewed (eg, lack of clarity or other issues affecting safety are usually much more concerning than issues of lesser consequence)
- Timeline (eg, whether the reviewer has the time to work through the misunderstanding/quality issue themselves)
- Complexity (eg, whether the reviewer is able to work through the quality issue in the document compared with sending it back to the sponsor)
- Resources (eg, whether a specialist is available on the regulatory agency side to review the document to help with the quality issue)

The impact of a document with a poorly written rationale can be significant. Some regulatory agencies could interpret a poorly written rationale as lack of transparency, which could then call the entire application into question (a "domino effect"), and documents with poor rationales would likely be flagged at each review step for extra investigation, which would affect the whole application. It was widely accepted that a poorly written rationale makes the entire review process more difficult and would have a negative effect on approval.

### Other document quality issues

Although we asked about the most common issues negatively affecting document quality, we

wanted to know if the regulatory reviewers encountered other issues that we had not specified.

Lack of transparency was identified as a key issue, particularly if the regulatory agency had experienced challenges with the sponsor or their applications previously. A lack of transparency and lack of clarity around the sponsor's objectives can raise regulatory reviewers' suspicions and give the impression that the sponsor is trying to overwhelm the reviewer with a mountain of data.

Transparency in terms of minutes from meetings with other regulatory agencies was also required, and a reluctance to provide these documents delays approval because it takes extra time to request them. The reviewers explained that it is important for them to see the concerns and requirements in other regions.

### Medical writers' influence on document quality and their role

We asked what influence the regulatory reviewers felt that medical writers had on document quality and the medical writer's role. The responses were extremely heartening and reflected the aims of the medical writing profession.

The regulatory reviewers felt that medical writers have a "great and positive influence on document quality; they help keep documents clear, as brief as they can be, and consistent." They felt that there is "definitely a difference when medical writers have been involved" in document production and that they can tell if inexperienced writers have been used, as they see a lack of attention to detail and adherence to standards.

The regulatory reviewers felt that "a professional medical writer is always welcome and is always needed" and believe that the importance and value of medical writers "continues to grow," to the extent that some regulatory agencies have established their own medical writing teams.

One of the reviewers summed up the situation beautifully: "I know that it is a very specific profession needing training. [Sometimes] we cannot tell who has written what in the applications or how much medical writers have been involved – it is invisible from the regulatory agency point of view. We don't need to know, we

just want something of good quality!"

### Anything else?

Finally, we asked a very open question – were there any other comments that the regulatory reviewers would like to make concerning document quality or the role of professional medical writers?

They explained that, beyond scientific expertise, medical writers should be involved in

document production to make the information understandable and usable for the reviewer. They emphasized that they cannot "transform a bad document" – if the information they are given is not understandable, they cannot reply to it, which they found very frustrating because their role is to encourage and facilitate drug development. Often, regulatory reviewers can see that there is excellent science and work behind the document, but because it has been written badly, they are forced to guess what the messages are. They believed that

although the role and work of medical writers may not be immediately visible to them, it was a "major" contribution.

Their final comment was that there was "no negative in having medical writers involved in document development – their influence and contributions are always positive."

### Looking forward

The objectives of the survey were to gain an understanding of how regulatory agencies perceive the value of medical writing and to learn where to focus the training and development of medical writers to maximize the value in, and skill set for, the preparation of regulatory documents.

The survey responses showed that many regulatory reviewers understand the role of medical writers, believe that they increase the quality of the documents sent to the agencies for review, and make the job of the regulatory reviewer easier. It is unsurprising that document quality is extremely important for regulatory reviewers. Participants reiterated that poor document quality can not only hamper the ability of the reviewer to provide an assessment (delaying the drug approval process), but also has the potential to bias reviewers against subsequent

The regulatory reviewers felt that medical writers have a "great and positive influence on document quality; they help keep documents clear, as brief as they can be, and consistent".

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submission documents from the same sponsor. There is a clear opportunity for medical writers to improve document quality, and the survey responses can also be used to inform how medical writers present themselves within their organizations – quality is clearly top of the regulatory reviewers' list of priorities and has been recognized by them as an area where medical writers add value.

Most satisfyingly, regulatory reviewers appreciated and recognized the work and importance of trained medical writers; thus, addressing regulatory reviewers' needs should continue to be a priority for the profession. Training must equip medical writers to lead teams that create documents that are concise and clearly present the message supported by the data. Perhaps even more focus should be given to team management and soft skills to allow medical

writers to lead and guide these teams so that the documents supporting submissions are as concise and strategic as possible to streamline and increase efficiency of the whole clinical development process.

The fact that the regulator reviewers, who are often time-poor, chose to take the time to help us to understand the role and value of medical writers is a testament to the importance of our profession and the expertise that trained medical writers bring to the development of regulatory documents and their associated teams.

### Acknowledgment

Thanks to Susan Krug, AMWA Executive Director, who provided significant support setting up the survey and with communication to survey participants.

### Author declaration and disclosures

The authors note no commercial associations that may pose a conflict of interest in relation to this article. The opinions expressed in this article are the authors' own and are not necessarily shared by their employers or AMWA.

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## The March 2023 edition



### **Clinical trials**

Medical writers and communicators are involved in clinical trials, from writing the trial protocol to reporting and publishing the trial results. This issue will focus on our roles, responsibilities, the documents we create, and our audience. Furthermore, we will also cover the regulations and best working practices governing documentations for clinical trials.

**Guest Editors: Raquel Billiones and Ivana Turek**

# Value of medical writing: The regulatory writer's perspective

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## Introduction

At its core, medical writing involves gathering, organizing, interpreting, and presenting complex information in a clear, concise, and coherent manner to a variety of audiences. Specific responsibilities can vary greatly across the industry, with roles and opportunities for medical writers constantly evolving. In this ever-changing environment, the role of regulatory medical writers is not always clear, and there is evidence to suggest that medical writers' contributions are not always fully understood or recognized.<sup>1</sup> To better appreciate the concrete value regulatory medical writers contribute to projects, teams, companies, and the wider biopharmaceutical industry, the American Medical Writers Association (AMWA) Executives Forum established a taskforce to define and quantify the value of medical writing. The 3 focus areas of the taskforce include writers' perceptions of their own value, regulatory agency perceptions of a writer's value, and other key topics related to the value of medical writers. This article describes the work of the subgroup tasked with determination of regulatory medical writers' perceptions of their own value. The main goals of this subgroup were to discover the views

## Abstract

The American Medical Writers Association formed a working group in 2020 focused on understanding and communicating the value that regulatory medical writers contribute to project teams, companies, and the wider research community. The working group developed a survey designed to gather information about the value that regulatory writers represent. The survey was targeted to regulatory medical writers, included 25 questions, and was administered by using SurveyMonkey. A total of 548 responses were received, and 522 of the respondents were active regulatory medical writers. The survey revealed that writers felt most valued when they were consulted or had their opinion

sought (n = 154, 30.8%), contributed to patients and the community (n = 89, 17.8%), and were well compensated (n = 80, 16.0%). Writers felt that their most valuable contributions to document preparation were clarity (n = 196, 44.1%) and organization (n = 80, 18%). Although most writers indicated that their employers provided sufficient opportunities for training and advancement (strongly agree, n = 131, 29%; agree, n = 197, 44.1%), writers also indicated they would benefit from additional training in leadership skills, project management, and collaborative skills/diplomacy. This insight is invaluable for shaping the future of the regulatory writing profession.

of regulatory medical writers regarding the nature of the value they contribute, identify aspects of the role that make writers feel most valued, and inquire about team feedback and dynamics. We also sought to identify additional skills, training, and opportunities for development that would benefit writers while also increasing the satisfaction of their teams.

## Methods

A 25-question survey was designed to evaluate multiple domains regarding the perceived value and contributions of regulatory medical writers. The intended time taken for respondents to complete the survey was 10 minutes, and the average duration of participation was determined to be less than 10 minutes. Many of the survey questions were multiple-choice questions, with some requesting a single answer and others allowing multiple answers (check all that apply). Additional questions allowed participants to rank their preferences. Other questions were presented in a 5-point Likert-scale format. One question was an open field that allowed participants to provide general comments on the topic at hand.

The survey was targeted to regulatory medical writers; the first question in the survey was binary (yes/no) and confirmed this status. The survey was administered by using SurveyMonkey

to members of the AMWA medical writing community, the European Medical Writers Association (EMWA) medical writing community, and the DIA Medical Writing Community. Working group members also distributed the survey to colleagues who were known to be regulatory medical writers and to partner companies who had regulatory medical writing groups who agreed to participate.

The survey was completely anonymous. However, some analyses utilized the anonymized participant number to track responses to different questions from the same participants in attempting to identify trends in the data.

## Participant profile

To better understand the characteristics of survey participants, several survey questions focused on demographics and work history. In response to the question, "Are you currently working (or have you worked within the past 5 years) as a regulatory medical writer?" we received a total of 548 responses, and 522 respondents (95.3%) confirmed current employment as regulatory medical writers. The second question in the survey inquired about work status. A total of 548 responses were also received for this question, and 488 (89.1%) were "employed," whereas 53 (9.7%) were "freelance or self-employed," 4 (0.7%) were "retired or unemployed," and

**Table 1. Analysis of employment for regulatory medical writers**

Type of employer	Responses (n)	Responses (%)
Pharmaceutical company	261	50.4
Clinical or contract research organization	118	22.8
Biotechnology company	56	10.8
Medical service company	29	5.6
Medical communication company	23	4.4
Full service provider/staffing company	15	2.9
Other (please specify)	13	2.5
Medical school or university	2	0.4
Medical marketing, advertising, or public relations agency	1	0.2

3 (0.5%) chose "other" as a category of employment. When asked about the type of company the respondents were employed by, a total of 518 responses were received, and the top 3 responses were:

1. Pharmaceutical company,
2. Clinical or contract research organization, and
3. Biotechnology company (Table 1).

When writers were asked about the larger group in which the regulatory writing group resided, the top response indicated that medical writing stood alone as a group (Table 2). However, as this is contrary to the experience of the members of the AMWA working group, it may be suggestive of some ambiguity inherent in the question, although it may be a predictable response in smaller companies or in clinical research organizations (Table 1; 22.8% of respondents). Some of the responses in the "other" category included "Clinical Affairs," "Data Science and Safety Reporting," "Document Solutions Group," and "Regulatory Documentation and Submissions."

The tenure of the regulatory writers who responded to the survey reflected long-term experience and the longevity of their dedication to the profession. A total of 444 writers responded to our question about years of writing experience, 242 (54.5%) of whom had more than 10 years of experience in the regulatory writing profession. A total of 84 (18.9%) respondents had between 6 and 10 years of writing experience, whereas 91 (20.5%) had between 2 and 5 years of experience and 27 (6.1%) had less than 2 years of experience. More than half of respondents had either a PhD degree (n = 206, 46.4%) or another advanced degree (n = 27, 6.1%); 147 (33.1%) respondents had a

master's degree, 56 (12.5%) had a bachelor's degree and 8 (1.8%) respondents specified a degree of "other." A total of 440 writers responded to a query regarding gender, with 330 (75%) writers identifying as women, 83 (18.9%) identifying as men, and 27 (6.1%) choosing "prefer not to say." Overall, professionals responding to this survey were highly educated, a high proportion were women, and most had long-term experience as regulatory writers. This is indicative of a profession that generally requires a high level of education and offers long-term employment and development. The paucity of respondents with less than 2 years of experience (6.1%) may reflect slow recruitment of writers or a slow growth rate for the pool of regulatory writing professionals. Alternatively, it could represent our inability to reach more junior medical writers. However, if this rate is representative of the industry at large, it is concerning, given the high growth rate for medical writing needs in the biopharmaceutical industry.

## Roles and career progression

We inquired about specific roles of medical writers to better understand how they are contributing, to learn what employers expect from medical writers, and to explore the relationship between required level of skill and the various roles of the writer. These survey questions categorized medical writing roles to reflect increasing levels of both technical skill and responsibility in order to understand the distribution of skills within the respondent pool (Table 3). The majority of respondents report involvement in activities beyond basic document preparation following a template. Most provide strategic guidance to teams and participate in some form of project management activity. Consistent with the long duration of tenure in the respondent pool, a relatively large proportion of respondents identified themselves with role C, representing a very high level of technical skill, knowledge, and responsibility.

To better illustrate the relationship between experience and role, we analyzed the responses for each role by years of experience (Figure 1). Although there was not an exact linear correspondence in the relationship between increasing years of experience and increasingly challenging roles, there was certainly a trend for professionals with longer tenure to fill the more challenging roles. Most individuals in the management/project management category had at least 10 years of experience in regulatory writing. These data indicate that regulatory writing is a highly technical discipline, and development of the necessary expertise to assume more strategic and management responsibilities appears to require several years to develop. This also suggests that regulatory writing is a career that offers long-term progression and development.

**Table 2. Organizational structure housing regulatory writing group**

Parent Group/Organization	Responses (n)	Responses (%)
Medical writing stand-alone group/function	198	38.2
Regulatory affairs	115	22.2
Clinical development	68	13.1
Clinical operations	52	10.0
Other (please specify)	32	6.2
Biostatistics or biometrics	18	3.5
Not applicable	16	3.1
Medical affairs	11	2.1
Strategic operations	4	0.8
Pharmacovigilance	2	0.4
Quality	2	0.4

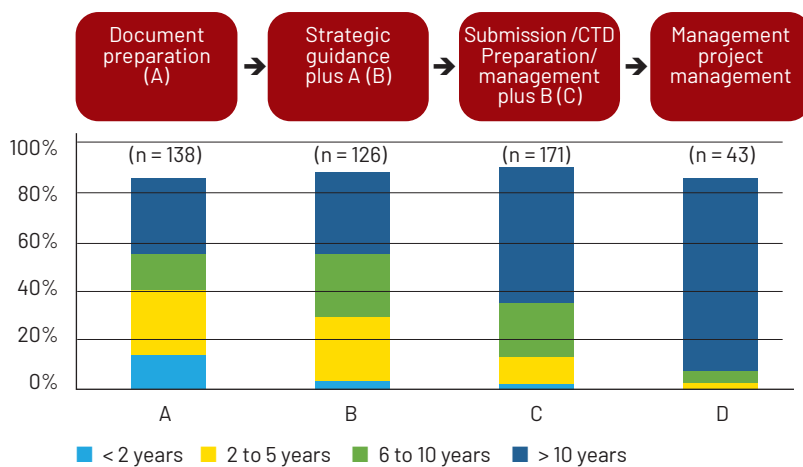
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**Table 3. Analysis of roles among regulatory writers**

Role	Responses (n)	Responses (%)
A. I Provide medical writing support/service to teams that is mainly focused on document preparation, using knowledge of templates, and ICH and other guidance(s).	138	27.6
B. I Provide support described in item A, but also provide strategic guidance to the teams.	126	25.2
C. I Provide Support In Items A and B and manage submissions documents and lead teams through CTD preparation routinely.	171	34.2
D. Management and/or project management.	43	8.6
Other (please specify).	22	4.4

CTD, Common Technical Document;

ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.



**Figure 1. Relationship between experience and roles**

CTD, Common Technical Document

**Value assessed by writers and teams**

Understanding and harnessing the skill set of experienced regulatory writers can keep writers engaged and make them feel satisfied and fulfilled. When writers were asked what made them feel most valued as a medical writer (and were forced to choose one answer), there was a clear leader among the options provided (Table 4). Medical writers felt most valued when their opinions were sought and when they were included in decision-making. This aspect of

feeling valued was chosen by more respondents than any other aspect, including compensation and other forms of recognition. Some responses in the “other” category were (1) “medical writers have unique skills that fill a need, unmet by any other discipline involved in healthcare”; (2) “coaching and training of new or junior writers”; and (3) “authorship and being consulted; having my ideas taken seriously and acted upon.”

The same question was posed with a requirement to rank these items and there was an

identical response pattern, except that “autonomy/flexibility” and “recognition” switched positions in the rate of response/rank. Interestingly, “career progression/job title/opportunity for movement” remained at the bottom of the list, with only 4.7% of respondents choosing this as their top ranked item.

Many writers felt that their tactical and technical skills were fully utilized, as well as their scientific and strategic skills (Figure 2; n = 495).

Additionally, most writers felt that the teams they supported fully recognized their value and skills. A total of 265 (53.5%) respondents agreed with this statement, whereas 107 (21.6%) strongly agreed. Interestingly, only 48 (9.7%) respondents disagreed, and 6 (1.2%) strongly disagreed. Consistent with these positive responses, most writers also felt that they were empowered by management to provide clear guidance to their team regarding the document development processes and felt they were included in most necessary meetings that enabled them to remain aware of strategic decisions that could impact document development (Figure 3; n = 495).

Although regulatory writers provide value to teams in many ways, we sought to understand the perception of writers themselves in terms of the value they contribute. When writers were asked to select one area in which they provide the most value in document preparation, there was a clear top choice (Table 5). Writers indicated that they contributed the most value by providing clarity in documents (44.1%), followed by “organization” (18.0%), “completeness” (10.1%), “accuracy” (9.9%), and “adherence to standards” (9.9%).

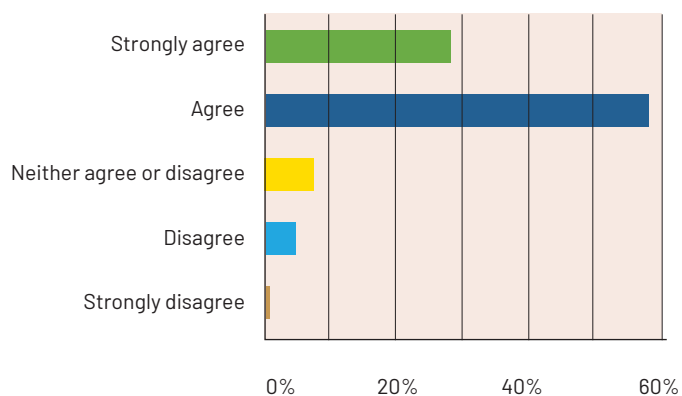
When writers were asked this same question but allowed to check all areas in which they contributed value, clarity was still at the top of the list (95.3% of writers included this in their selections), and organization was still in second place (90.8% of writers included this in their selections).

A general comment regarding the value of medical writers was provided by 102 (18.6%) writers. Key themes in the responses were the value provided to teams to ensure that the documents will lead to a successful submission. An example is this response: “The quality and delivery time of regulatory documents improved dramatically when my employer established a medical writing department within Clinical Operations.” The responses indicate that clear, well-written, and accurate messages are an important part of the medical writer’s role and

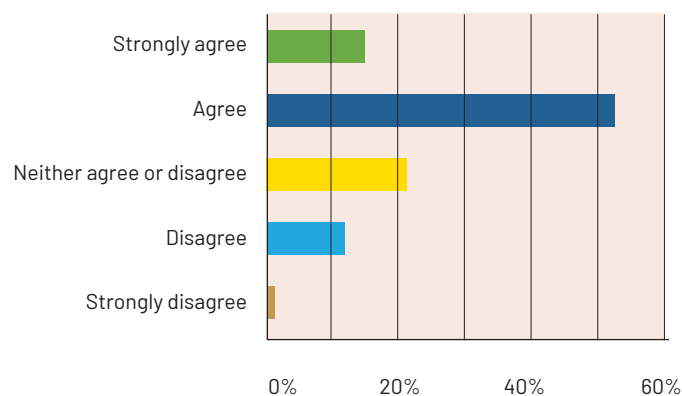
**Table 4. What makes regulatory writers feel valued**

What makes me feel valued?	Responses (n)	Responses (%)
Consulted/opinion sought/ decision-making	154	30.8
Making a contribution to patients/community	89	17.8
Compensation	80	16.0
Involvement in scientific research/ developing your own scientific knowledge	77	15.4
Autonomy/flexibility	32	6.4
Recognition	31	6.2
Career progression/job title/ opportunity for movement	28	5.6
Other (please specify)	9	1.8

**Technical and tactical skills**

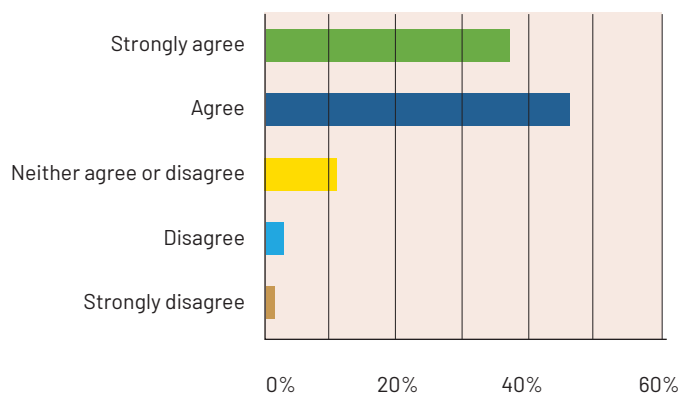


**Scientific and strategic skills**

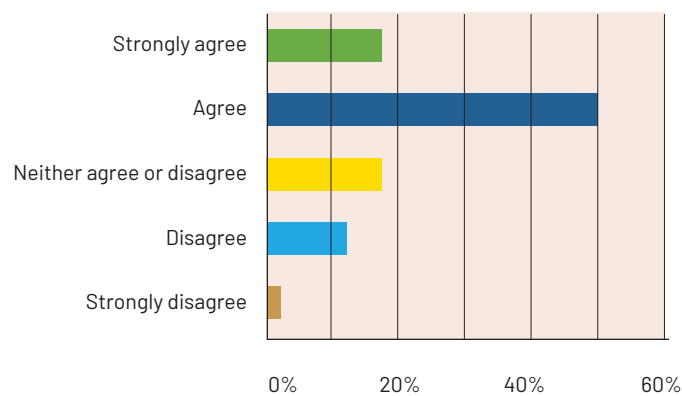


**Figure 2. Utilization of skill sets**

**Empowered by management**



**Included in key meeting**



**Figure 3. Key determinants of success**

## REPRINT

**Table 5. Areas in which writers provide value in document preparation**

Area of document preparation	Responses (n)	Responses (%)
Clarity	196	44.1
Organization	80	18.0
Completeness	45	10.1
Accuracy	44	9.9
Adherence to standards	44	9.9
Explanation of rationale	22	5.0
Brevity	9	2.0
Formatting	4	0.9
Linking	0	0.0

**Table 6. Skills and contributions recognized most frequently by teams**

Skill recognized by team <sup>a</sup>	Responses (n)	Responses (%)
Leadership, including management of the process and maintenance of timelines	148	32.8
Collaboration and flexibility	116	25.7
Providing strategic guidance on document development and/or submissions	79	17.5
Writing skills with respect to vocabulary and sentence structure, grammar, improved readability, etc.	34	7.5
Comment resolution and achievement of consensus	26	5.8
Problem-solving	19	4.2
Quality control and accuracy	19	4.2
Input to study design and project decisions	5	1.1

<sup>a</sup>Survey respondents had to choose only one skill

that this is best achieved by integration into project teams. A response that expressed this was, "Clinical-regulatory writers are critical members of the team who guide development of documents with an overall perspective for program strategy and a document that is complete, accurate, and well-written." The responses indicate that this enables the medical writer to lead team collaboration, ensure that documents support project goals, and drive the process to speed delivery and ensure high quality/regulatory compliance. A representative response was, "We take ownership and drive/lead the document through the process, and only by guiding the team do we get through it." Several writers stated that the role of the medical writer is underappreciated. Insight is provided by this response: "Much of the value can go unnoticed by management as it is difficult to measure what good clinical-regulatory writers provide to documents and the document completion process."

Pivoting to inquiry regarding the value that teams perceive as writers' greatest contributions,

the skills that writers felt they were most frequently recognized for were leadership and collaboration skills (Table 6), both considered to be behavioral skills or "soft skills" rather than technical skills directly related to writing.<sup>2</sup>

When asked to rank the frequency of recognition of skills, the 3 top responses remained consistent, with all the other skills/behaviors ranking at least 5% beneath the third most highly ranked skill (Table 6; 17.5%, providing strategic guidance on document development and/or submissions).

Interestingly, when this line of inquiry was reversed and we asked writers to provide information about constructive feedback they received from teams about areas for improvement, responses in the "other" category represented the highest proportion of responses (Table 7; n = 110, 24.4%). However, the most common entries in the "other" category open field were "none" and "not applicable," and there was no consistent trend, suggesting that inclusion of that option/field may have detracted from the

precision of the data. The next 2 most frequent responses were (1) leadership, including management of the process and maintenance of timelines, and (2) improve flexibility. Therefore, the 2 items writers felt they were most frequently recognized for doing well were also the 2 specific items for which they felt that teams requested improvement or better support. These data suggest that leadership and collaboration should be key areas of focus for writer development.

When writers were asked to rank (from 1 to 7) the 7 skills for which teams had requested better support ("other" was not included), leadership and lack of flexibility were still cited as the top areas for improvement (Table 7).

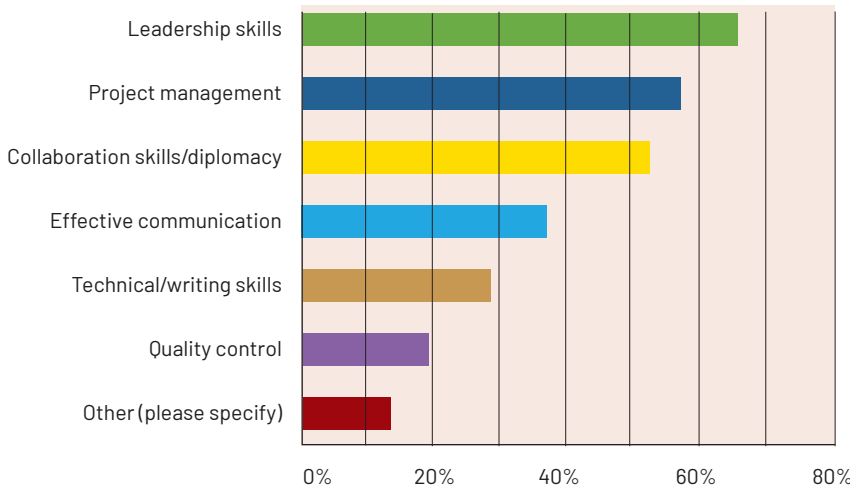
### Training opportunities and needs

One of the main reasons for conducting this research was to identify potential gaps between medical writer skills and team and/or employer expectations. Although this investigation relies on information gathered from regulatory writers and not teams or employers, we can compare our results with research conducted by another group<sup>2</sup> as it relates to the pharmaceutical medical writing competency model.<sup>3</sup> According to information Heisel-Stoehr and Schindler obtained from 73 job advertisements for regulatory medical writers, "science" and the "comprehension of scientific concepts" were important technical skills cited in 78% and 92% of those job advertisements, respectively.<sup>2</sup> Our survey suggests that writers are not primarily recognized for such contributions during document development. Additionally, writers themselves felt that their most important contributions to document development were clarity and organization, technical writing skills that may or may not require a deep scientific understanding. On the other hand, the 73 job advertisements described by Heisel-Stoehr and Schindler cited "leadership and team working skills" as the most frequently (62%) mentioned behavioral skill/skills for regulatory writers.<sup>2</sup> In fact, our survey results find that these are the 2 areas for which writers are most frequently recognized by teams for commendable performance (Table 6).

Although most writers in our survey felt that their employers provided them with sufficient opportunities for training and development to enable success and advancement (agree, n = 197, 44.1%; strongly agree, n = 131, 29.3%), there were others in the survey who felt neutral (neither agree or disagree, n = 78, 17.4%) and

**Table 7. Constructive feedback from teams**

Skill that needs improvement	Responses (n)	Responses (%)
Other (please specify)	110	24.4
Leadership, including management of the process and maintenance of timelines	79	17.5
Lack of flexibility	62	13.7
Compliance with procedures	61	13.5
Comment resolution and achievement of consensus	45	10.0
Writing skills with respect to vocabulary and sentence structure, grammar, improved readability, etc.	36	8.0
Quality control, too many errors	36	8.0
Collaboration	22	4.9



**Figure 4. Areas desired for more training/learning.**

some who disagreed (n = 30, 6.7%) or strongly disagreed (n = 11, 2.5%). These results speak well of management efforts to keep writers engaged and developing. When writers were asked to identify areas in which they needed more opportunities to learn, there was a significant focus on (1) leadership skills, (2) project management, and (3) collaborative skills/diplomacy (Figure 4). Once again, the notion that behavioral skills or “soft skills” play a prominent and crucial role in the successful execution of the duties of the regulatory writer is reinforced throughout the results of our survey.

**Summary**

Results from the survey encompassing 548 respondents with regulatory medical writing experience revealed key information that is useful for understanding the value that medical writers bring to an organization and useful for further

defining job responsibilities and skills needed for regulatory medical writers. Regulatory medical writers are highly educated professionals whose development to attain the skills necessary for leading regulatory submission preparation and managing projects and teams requires several years. The role requires both technical/tactical skills and scientific/strategic skills. Most regulatory medical writers report that their duties extend beyond basic document preparation following a template to include providing strategic guidance to teams and participating in some form of project management activity. Project teams rely on medical writers for leadership and collaborative skills. Medical writers recognize these soft skills as both their key contributions and their key training needs. Data suggest that regulatory medical writers feel most valued when their opinions are sought and when they are included in decision-making.

**Acknowledgement**

Thanks to Susan Krug, AMWA Executive Director, who provided significant support setting up the survey and with communication to survey participants. We also wish to thank the membership of AMWA, EMWA, and the DIA medical writing communities for their participation in the survey.

**Author declaration and disclosures**

The authors note no commercial associations that may pose a conflict of interest in relation to this article. The opinions expressed in this article are the authors’ own and not necessarily shared by their employers or AMWA.

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# Winner of the Geoff Hall Scholarship Essay Competition

Dear All,

The Geoff Hall Scholarships are given in honour of the former President of EMWA. Geoff was a very special person, an extremely valued member of EMWA, and a very good friend to many EMWA members. He firmly believed that the future of EMWA lies in our new and potential members, and so it's a very fitting legacy that we have the Scholarship Awards in his memory. The scholarships are awarded annually on the basis of an essay competition, and the title of this year's essay was "The Ethics of Medical Writing". The committee has the ability to award up to two scholarships each year. This year we decided to award a single

## FOR CORRESPONDENCE



**Lisa Chamberlain James**  
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scholarship – to Sampoorna Rappaz.

Sampoorna received her master's degree in human genetics from the University of Leeds, UK, in 2008 and went on to complete her doctoral training in cancer biology at the University Children's Hospital Zurich, Switzerland, in 2014. After a career break, she restarted her professional life as a freelance scientific editor in 2019. She found a deep satisfaction in helping authors effectively communicate complex and important science.

During 2020–21, as our world was awash with health-related information, she became even more keenly focussed on training to become a professional medical communicator.

Sampoorna's winning essay is presented below, and we wish her the very best at the start of her very promising medical writing career. For those of you inspired to pick up your laptop, this year's essay title is "How to Keep Your Reader Interested From Start to Finish".

I hope to read your essays soon, and stay safe all, until we see each other at the next EMWA conference.

Bestest,  
**Lisa**

## Ethics in medical writing: Who shall I be?

It is only right that I begin this essay on professional ethics with a pertinent disclosure: For several years I considered medical communications as an unethical profession. The book *Bad Pharma* by Ben Goldacre was my introduction to the business and practice of medical communications.<sup>1</sup> In it, he portrays publication planning as an inherently unethical process that is rife with distortion and deception, uses the term "ghostwriting" as a synonym for medical writing, and at one point refers to professional medical writers' associations as "ghostwriters' associations" (p.325). Comfortably seated on the moral high horse as an academic, I accepted these statements as facts – after all, what more could I expect from a profit-driven industry?! This was 2016. In 2019, I was signing up to become a member of EMWA.

In those three years, having been on the receiving end of a barrage of medical information as a parent and a patient caregiver, I came to

deeply appreciate the importance of effective medical communication. So much so that I decided to become a medical communicator. Curiosity led me to EMWA, but what got me to stay were its ghostwriting position statement and its joint position statement (with American Medical Writers Association [AMWA] and International Society for Medical Publication Professionals [ISMPP]) on the role of professional medical writers.<sup>2,3</sup> My prejudices crumbled. I had a lot to unlearn and a lot to learn. Through attending conferences and workshops, I gained a deeper understanding of the roles and responsibilities of *professional* medical communicators.

To earn the right to be called a professional, one must accept the ethical responsibilities that go along with that position.<sup>4</sup> Ethical principles are moral values interpreted within a specific



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context.<sup>4</sup> They state abstract requirements.<sup>5</sup> Onara O'Neill, an eminent philosopher with influential writings on ethics, argues that "*Ethical principles are always needed in the middle of lives and activities in which action and practices, policies and institution are constrained in multiple ways,*" (p. 124).<sup>5</sup> Medical communicators face many constraints: guidelines, regulations, laws, personal morality, conflicts of interest, target audience, business partners, healthcare professions, and even society at large. Ethical codes allow for nuanced navigation of complex situations involving multiple stakeholders.

AMWA's code of ethics, with its broad scope,





acts as a basic code for all professional medical communicators (hereafter, communicators).<sup>6</sup> ISMPP's code of ethics is instructive for communicators involved in the development and dissemination of scientific publications.<sup>7</sup> These professionals also adhere to the recommendations provided by the International Committee of Medical Journal Editors (ICMJE) and the Good Publication Practice (GPP) guideline, which prioritise integrity, transparency, and accountability.<sup>8,9</sup> For accurate, complete, and clear presentation of medical research, communicators use relevant reporting guideline(s) available from the Enhancing the QUALity and Transparency Of health Research (EQUATOR) network.<sup>10</sup> The Committee on Publication Ethics (COPE) provides guidance on ethical publication processes to help authors, editors, and communicators make ethically sound decisions.<sup>11</sup> The recently published AMWA-EMWA-ISMP statement on standardizing medical publication processes offers solutions that uphold data integrity and enable transparent practices.<sup>12</sup>

Communicators working on regulatory documentation primarily follow regulatory authority-issued guidelines that are based on ethical principles. In addition, gaining a deeper

So that is who  
I shall be: an  
ethical, virtuous,  
trustworthy  
professional  
medical  
communicator.

Never a  
ghostwriter.

understanding of the ethical principles behind Good Clinical Practice (GCP) is recommended. This helps in identifying ethical situations and in prioritizing the ultimate goal of clinical research:

to improve healthcare while always respecting the dignity of human life.<sup>13,14</sup> Also, the Regulatory Affairs Professionals Society (RAPS) code of ethics lists core values that all regulatory professionals must embody.<sup>15</sup>

Communicators developing materials for promotional purposes and medical education abide by the ethical codes and latest regulations that pertain to the interactions between healthcare professionals and the pharmaceutical and

medical technology industries, such as, the codes developed by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and MedTech Europe.<sup>16–18</sup> The codes of ethics of professional associations of writers and journalists who specialise in reporting science- or health-related news (eg., Association of Health Care Journalists) make for excellent guides for communicators developing any content for the lay audience.<sup>19</sup>

Professional organisations' codes and legal compliance checklists lay out minimum ethical requirements; therefore, communicators should aim to go above and beyond these in their

work.<sup>4,20</sup> Communicators should aim to define their personalised standard operating procedures and share these with prospective contractors and clients – a practice that is recommended for freelancers,<sup>21</sup> who often do not receive compliance training from their clients.<sup>16,22</sup> To facilitate ethical decision-making, communicators could use the five steps outlined in the “RIGHT model”: **R**ecognise the ethical situation, **I**nvestigate the facts, **G**auge the situation, **H**andle the situation, and **T**ailor the decision.<sup>21,23</sup> Communicators are more than the sum of the ethically sound documents they develop; their ethical principles must extend to all aspects of their professional behaviour. *The Elements of Ethics for Professionals*, a book favoured by the ethics workshop leaders at AMWA, elaborates on 11 virtue-based behaviours that an ethical professional should constantly practice:<sup>4,13,20</sup>

- Working with integrity
- Doing no harm
- Being respectful
- Benefiting others
- Being cautious
- Being compassionate
- Promoting fairness
- Encouraging self-determination
- Being loyal
- Aiming for excellence
- Using sound judgment

Maintaining an ethical practice is difficult; it requires diligence and moral fortitude. It may not even guarantee an increase in trust in the profession. According to O’Neill, we are living within a “culture of suspicion”.<sup>24</sup> Goldacre wrote that “ghostwriters” could not be trusted to adhere to “a weak new voluntary code with no teeth” (p. 305).<sup>1</sup> The authors of a recent article in the journal *JAMA Oncology* speculated that an increase in medical writing assistance is a cause for concern because “medical writers may unduly influence the interpretation of [clinical] trials”.<sup>25</sup> In fact, neither of these statements hold up to systematic scrutiny.<sup>22,26,27</sup> So why bother? O’Neill reminds us that our obligations are clear even if trust is withheld.<sup>5</sup> We must always do what is fundamentally ethical. She recommends that instead of asking for trust one should strive to *be trustworthy*, which she defines as being reliable, honest, and competent.<sup>28</sup> So that is who I shall *be*: an ethical, virtuous, trustworthy professional medical communicator. Never a ghostwriter.

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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](http://www.ema.europa.eu).

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## Regulatory harmonisation of clinical trials in the EU: New Clinical Trials Information System launched

January 25, 2022

**O**n January 31, 2022, the Clinical Trials Regulation (CTR) will come into application harmonising the submission, assessment, and supervision processes for clinical trials in the European Union (EU). The backbone of the changes brought about by the CTR is the new Clinical Trials Information System (CTIS). CTIS is a single entry point for sponsors and regulators of clinical trials for the submission and assessment of clinical trial data which includes a public searchable database for healthcare professionals, patients and the general public.

In the past, sponsors had to submit clinical trial applications separately to national competent authorities (NCAs) and ethics committees in each country to gain regulatory approval to run a clinical trial, and registration and posting of results were also separate processes. With CTIS, sponsors can now apply for authorisations in up to 30 EU/EEA countries at the same time and with the same documentation. Publication of the trial information is built in the system.

The application of the CTR and the go live of CTIS – in the EU and the European Economic Area (EEA) countries (Iceland, Liechtenstein

and Norway) – will strengthen Europe's position as an attractive location for clinical research. The new regulation streamlines the application and supervision of clinical trials, and their public registration: all clinical trial sponsors will use the same system (CTIS) and follow the same process to apply for the authorisation of a clinical trial, no matter where they are located and with which NCA or ethics committee they are dealing. The new system has a dedicated secure workspace for trial sponsors where they can apply for and manage their clinical trial applications. There is a similar secure workspace for the authorising authorities, who can easily interact with the sponsor and quickly collaborate and exchange information with other authorities.

Because transparency is a major feature of the CTR, CTIS also includes a searchable public website, that will prospectively contain detailed information on, and outcomes of, all clinical trials authorised through the system.

The CTR foresees a 3 year transition period. Member States will work in CTIS immediately after the system has gone live. For 1 year, until January 31, 2023, clinical trial sponsors can still

choose whether to submit an initial clinical trial application in line with the current system (Clinical Trials Directive) or via CTIS. From January 31, 2023, submission of initial clinical trial applications via CTIS becomes mandatory, and by January 31, 2025, all ongoing trials approved under the current Clinical Trials Directive will be governed by the new Regulation and have to be transitioned to CTIS.

The authorisation and oversight of clinical trials is the responsibility of EU/EEA Member States while the European Medicines Agency (EMA) is responsible for maintaining CTIS. The European Commission (EC) oversees the implementation of the Clinical Trials Regulation.

### Accelerating Clinical Trials in the EU (ACT EU) for better clinical trials that address patients' needs

Building on the application of CTR and CTIS, the EC, the Heads of Medicines Agencies (HMA) and EMA also launched the Accelerating Clinical Trials in the EU (ACT EU) initiative that seeks to transform how clinical trials are initiated, designed, and run. The aim is to further develop the EU as a focal point for clinical research, 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 citizens expect. The ACT EU strategy paper published on January 13, 2022 lists the ten priority actions for 2022/2023, including enabling innovative trial methods, establishing a multi-stakeholder platform, and supporting the modernisation of good clinical practice. Together, they will contribute to achieving the ambitious goals for innovation in clinical trials set out in the European medicines agencies network strategy (EMANS) to 2025 and the European Commission's Pharmaceutical Strategy.



## New EU rules for safe and high-quality medicines for animals become effective

January 28, 2022



**T**oday, the Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6) becomes applicable. It contains new measures for stimulating innovation and increasing the availability and access to safe and high-quality veterinary medicines for veterinarians, farmers and pet owners to treat and prevent animal diseases and also supports the EU action against antimicrobial resistance (AMR). The tools and systems introduced by the new Regulation will ensure wider access to information on medicines for animals to all stakeholders and will also provide for an enhanced monitoring of suspected side effects.

The new rules put in place a range of measures to limit the development of AMR, while ensuring that necessary treatments remain available for animals and people, a true “One Health” approach. The new provisions foresee that preventive antimicrobial use is permitted only in exceptional circumstances and introduce the possibility to restrict or prohibit the use of important antimicrobials in animals, reserving the most important of them for treatment of certain conditions in humans.

The new Regulation contains measures that will simplify regulatory processes, striving to reduce administrative burden for current marketing authorisation holders and developers of new

and innovative veterinary medicines to further encourage medicine innovation and development.

For the first time, information about all veterinary medicines authorised in the EU and EEA countries will be available on a central website.

Another key novelty is that from now on veterinary prescriptions will be valid throughout the EU. Furthermore, a common logo was established to facilitate identification of online retailers, which are authorised to sell veterinary medicines that require prescription. Online retailers will have to display the common logo on their website and link it to the relevant EU/EEA national authority website. These authorities will list all registered online medicine retailers in their country on their websites.

During the lead-up to the entering into application of the Regulation, EMA has revised its procedures and regulatory and scientific guidance documents. The Agency has also led, in collaboration with the Member States and stakeholders, the development and implementation of the IT systems required by the Regulation:

1. Union Product Database
2. Union Pharmacovigilance Database
3. Manufacturing and Wholesale Distribution Database

The Union Product Database gathers information on all veterinary medicines authorised in EU/EEA countries and will enable some post-authorisation procedures. The system has been set up and will be maintained by EMA in collaboration with the Member States and the EC. While EMA and the regulatory network are finalising the upload of product data, activities to improve the data quality have also been initiated.

The Veterinary Medicines information website will provide public access to the data held in the Union Product Database. It is the first website that provides details on all veterinary medicines authorised in the EU and EEA. The website will enable veterinary healthcare professionals and all interested users to find out in which EU Member States and EEA countries a specific veterinary medicine is available, or to find information that could help identify potential treatment alternatives. At the same time, by providing a single source of up-to-date information on the availability of veterinary medicines in the EU it will support a better functioning of the single market.

The Union Pharmacovigilance Database was launched as an enhanced and upgraded EudraVigilance Veterinary (EVVet3) system for the exchange and processing of suspected adverse reaction reports related to veterinary medicines authorised in the EEA. EVVet3 is supplemented by an upgraded analytics tool and new functionality to support pharmacovigilance monitoring activities. Integrating all these components, the Union Pharmacovigilance Database is the key tool for the continuous monitoring of the safety of veterinary medicines after they are authorised.

The Manufacturing and Wholesale Distribution Database includes information on the granting, suspension or revocation by competent authorities of any manufacturing authorisation, wholesale distribution authorisation, certificates of good manufacturing practice and registration of manufacturers, importers and distributors of active substances for both veterinary and human domains. The system launched today is an enhanced and upgraded version of EudraGMDDP, the EU database of manufacturing authorisations and certificates of good manufacturing practice, with changes affecting both the veterinary and the human domains.

More information on these databases can be found on the Veterinary Medicinal Products Regulation page.



## European medicines regulatory network adopts EU common standard for electronic product information

February 22, 2022

**T**oday, The European Medicines Regulatory Network has adopted a Common Standard for the electronic product information (ePI) on medicines in the EU. This will pave the way for wider dissemination of the unbiased, up-to-date information on all medicines available to patients in the EU through an ever-expanding range of electronic channels.

The product information (PI) of a medicine includes the package leaflet for patients and the summary of product characteristics (SmPC) for healthcare professionals. These documents accompany every single medicine authorised in the EU and explain how it should be used and prescribed.

The EU ePI Common Standard will support the provision of harmonised electronic information on medicines within the EU and is a step

towards improved delivery of information for patients, consumers and healthcare professionals to aid their informed decision-making.

The ePI can be updated immediately, as soon as new information becomes available. The structured nature of ePI will also offer new opportunities to personalise the product information to individual needs and to make it more easily accessible to users with diverse abilities. Future developments of the ePI could include functionalities such as automatic update notifications, access to supportive videos or audio content and online adverse-reaction reporting tools.

The Common Standard was one of the key deliverables of an ePI project run by the EMA, national competent authorities (NCAs) and the EC in 2021. A follow-on pilot project supported

by the EU's funding programme EU4Health will now focus on developing tools and guidance to pilot the use of ePI prior to implementation. EMA will publish regular progress updates and will share the results with patients, healthcare professionals, academia, and the pharmaceutical industry.

The adoption of the Common Standard is in line with the ePI key principles which were established following stakeholder consultations and guide the development of the ePI in the EU. The EU ePI Common Standard is based on Fast Healthcare Interoperability Resources (FHIR), an international technical standard describing data formats and elements and an application programming interface for exchanging electronic health records. FHIR also supports the exchange of information about medicinal products, substances, and related referential data in the European medicines regulatory network.

## New medicine for rare type of eye cancer

February 25, 2022

**E**MA has recommended granting a marketing authorisation in the EU for Kimmtrak (tebentafusp; applicant, Immunocore Ireland Limited), a monotherapy for the treatment of adult patients with uveal melanoma, a rare type of eye cancer.

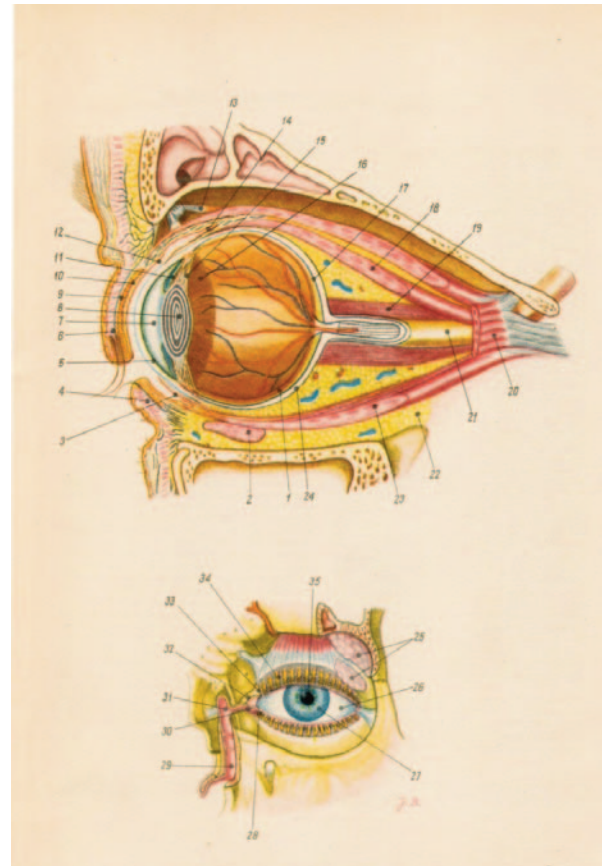
Uveal melanoma is a rare and aggressive disease in which cancer cells form in the tissues of the eye. Signs of uveal melanoma include blurred vision or a dark spot on the iris. Patients with uveal, or ocular, melanoma often have a poor prognosis as the disease can resist treatments and spreads quickly through the body with the liver being the most frequent site of metastasis (cancer spreading to other parts of the body). Once the disease has spread, many patients survive less than a year.

Currently, the most widely used first-line treatment options for non-metastatic disease for this cancer are surgery, radiation therapy, and enucleation (procedure by which the entire eye is removed). The condition is found primarily in the population with light skin pigmentation and light-coloured eyes. It is estimated that uveal melanoma affects between five and eleven patients per million.

Tebentafusp, the active substance of Kimmtrak, is a type of treatment called a bispecific fusion protein. It works by helping immune cells to get close enough to the cancer cells to attack them. The treatment can be used in adult patients who are human leukocyte antigen (HLA)-A\*02:01-positive and have unresectable (cannot be removed surgically) or metastatic uveal melanoma.

EMA's human medicines committee (CHMP) reviewed the application for marketing authorisation under an accelerated timetable to enable faster patient access to this medicine in view of the high unmet medical need. Kimmtrak had been designated as an orphan medicinal product on February 19, 2021.

The CHMP based its recommendation on data from a randomised Phase 3 pivotal study and a supportive study. The pivotal study included 378 previously untreated patients with advanced uveal melanoma, of whom 252 patients were randomly selected to receive tebentafusp and 126 patients were in the control group and received one of three already established therapies for the condition (dacarbazine, ipilimumab or pembrolizumab). Tebentafusp was administered to patients via intravenous infusion. The main measure of effectiveness was overall survival (how long the patients lived). The study showed that Kimmtrak prolonged patients' lives: the median overall survival was 21.7 months for patients receiving tebentafusp and 16 months for patients in the control group. The most common side effects observed in clinical trials were skin rashes, fever, and itching.



The opinion adopted by the CHMP is an intermediary step on Kimmtrak's path to patient access. The opinion will now be sent to the EC for the adoption of a decision on an 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 establishes Cancer Medicines Forum with academia to optimise cancer treatments in clinical practice

March 31, 2022

**E**MA, in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), has launched the Cancer Medicines Forum (CMF). Bringing together representatives from academic organisations and the European medicines regulatory network, the forum aims at advancing research into optimising cancer treatments and will contribute to foster high standards in cancer care in the EU.

Since its establishment in 1995, EMA has

reviewed and recommended for approval over 170 cancer medicines that have gone on to play an important role in the treatment and management of various types of cancers. The field of oncology has seen the emergence of major innovations in recent years, including the arrival of personalised medicines, immunotherapies, and advanced therapy medicinal products. Such innovations have helped cancer patients across Europe by offering them new tools in their fight against the disease. However, at the time new

medicines enter the market, there is an opportunity to improve many aspects with respect to their optimal use and integration into the existing array of treatments. Addressing these opportunities for treatment optimisation may require the conduct of studies to collect robust data to further guide clinical practice.

The CMF met today for the first time to discuss challenges around the research into optimisation of treatments, such as dose-optimisation and similar approaches tailored to the characteristics of the patient and the disease. Meetings will be organised quarterly, including

## New gene therapy to treat adult patients with multiple myeloma

March 25, 2022

**E**MA has recommended a conditional marketing authorisation in the EU for Carvykti (ciltacabtagene autoleucl; applicant, Janssen-Cilag International NV) for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies and whose cancer has worsened since they received their last treatment.

Multiple myeloma is a rare cancer of the plasma cells, a type of white blood cell that produces antibodies and is found in the bone marrow. In multiple myeloma, the proliferation of plasma cells is out of control, resulting in abnormal, immature plasma cells multiplying and filling up the bone marrow. When plasma cells become cancerous, they no longer protect the body from infections and produce abnormal proteins that can cause problems affecting the kidneys, bones, or blood.

Despite the development and approval of a range of new medicines for the treatment of multiple myeloma over the past few years, there are limited therapeutic options for patients who have already received three major classes of drugs (immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies) and whose disease has come back or no longer responds to these medicines. Therefore, new medicines are needed for these patients.

Ciltacabtagene autoleucl, the active substance of Carvykti, is a chimeric antigen receptor (CAR)-T cell medicine. It is an advanced therapy for cancer that is based on collecting and modifying patient's own immune T-cells to

create a patient personalised treatment that is infused back.

Carvykti had been designated as an orphan medicinal product and 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.

The main study on which the recommendation for a conditional marketing authorisation is based, is a single arm, open-label, multicentre



clinical trial. The study investigated the efficacy and safety of ciltacabtagene-autoleucl in 113 adult patients with relapsed and refractory multiple myeloma who had received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and who didn't respond to the last treatment regimen. About 84% of patients enrolled in the study responded to the treatment

with a durable response (a period without disease signs or symptoms after treatment). Around 69% showed a complete response, meaning the signs of cancer disappeared.

The most common side effects are cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms, infections and encephalopathy, i.e. a brain disorder. The consequences of CRS can be life-threatening and, in some cases, even fatal. Furthermore, other important safety aspects are neurologic toxicity, prolonged cytopenia and serious infections. Monitoring and mitigation strategies for these side effects are described in the product information and in the risk management plan that is an integral part of the authorisation.

Additional risk minimisation measures required from the marketing authorisation holder will ensure that centres that dispense the therapy are qualified to recognise and manage CRS and neurotoxicity associated with the treatment of Carvykti.

Additional efficacy and safety data are being collected through the submission of follow-up data from the main clinical trial and through an ongoing study that will compare the efficacy and safety of the medicine with standard triplet regimens in patients with relapsed and lenalidomide-refractory multiple myeloma.

Because Carvykti is an advanced-therapy medicinal product (ATMP), it was assessed by the Committee for Advanced Therapies (CAT), EMA's expert committee for cell- and gene-based medicines, and EMA's CHMP, which recommended approval based on the CAT assessment.

representatives of key academic organisations from EMA's Healthcare Professionals Working Party. The results of these discussions will support the prioritisation of actions to fight cancer included in the Regulatory Science Strategy to 2025 and the Academia Collaboration Matrix Action Plan. Following a 1-year pilot phase, the composition and working procedures of the forum will be re-evaluated.

Further information about the Cancer Medicines Forum will be published on EMA's academia webpage.



# Regulatory Public Disclosure

## SECTION EDITORS



Sam Hamilton  
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## Getting to grips with the EU CTR and CTIS

### Editorial

A great deal has happened in the world of regulatory public disclosure in Europe in 2022 with the EU Clinical Trials Regulation (CTR) 536/2014 coming into force at the end of January 2022. We collectively attempt to assimilate knowledge and experience of protocols prepared for and conducted under the Regulation as a first learning step, and to appreciate the nuances of how trials registered under the CTR will be entered and displayed in the Clinical Trials Information System (CTIS).

There are multiple CTR impacts on the

documents traditionally written by medical writers, many of which will be subject to public disclosure. Although impacts are incorporated into publicly available resources such as the TransCelerate Common Protocol Template (<https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/>) which can be used to author protocols, and CORE Reference ([www.core-reference.org](http://www.core-reference.org)) which can be used to inform clinical study report (CSR) authoring, a number of important EU CTR-related considerations are worthy of further exploration here:

**1** Before obtaining informed consent, potential trial participants should receive information in a prior interview in language they can understand. Additional documentation about the prior interview will be required. Adequate time for participants to consider their decision is needed and separation between this interview and the actual consent interview is required. This poses a number of legitimate questions. Would MWs be involved in preparation of such prior interview document templates? Where and how should timing of the prior interview and the consent interview be captured? The interval between interviews may need to account for different types of trial design, some of which can be highly complex, and difficult to understand. Would some participants require more time than others? There are no straightforward answers, and many will be study-specific, but this should raise awareness of the need to consider developing processes to support this requirement.

**2** The protocol authorised under the CTR must define the purposes and conditions for which the data of the participants will be processed. The participants should be properly

informed on the processing of their personal data in the Informed Consent Form (ICF).

**3** A serious breach of the protocol or the CTR is a breach likely to affect to a significant degree the safety and rights of participants, or the reliability and robustness of the data generated in the clinical trial. Serious breach reporting in CTIS is to be no later than 7 days from becoming aware of the breach. The process for serious breach reporting should be described in the protocol and any actual serious breaches will need to be reported in the CSR. Considering that systematic serious breaches affecting the data may be discovered after the operational conduct of the study has concluded, the serious breach process development or review should involve input from team members outside of clinical operations, and should include functions as broad as programming, biostatistics, and medical writing. It is also worth noting that if a systematic serious breach occurs in a multi-regional clinical trial outside of the EU, if there was potential for that breach to also occur in the EU, then this must also be reported in CTIS within the 7-day timeframe. All this is relevant for clinical trial reporting, and would appear in publicly disclosed documents.

Chair: Sam Hamilton  
Committee members: Margaret Bray, Vivien Fagan, Zuo Yen Lee, Alison McIntosh  
Advisor: Art Gertel  
Supporting member: Raquel Billores (MD-SIG)

### THE CORE REFERENCE PROJECT

The Clarity and Openness in Reporting: E3-based (CORE) Reference Project aims to provide continuous professional development for the regulatory medical writing community through open-access resources and intelligence dissemination on clinical study reporting and public disclosure of clinical-regulatory documents.

[contact@core-reference.org](mailto:contact@core-reference.org)

**4** A summary of study results needs to be submitted in CTIS within a year from the end of the trial (and within 6 months for paediatric trials), and this should include a summary understandable to lay persons. Content for the summary report is in Annex IV and for the lay summary in Annex V of the CTR. If it is not going to be possible to submit a





**Some members of the CORE reference Project Committee at the EMWA Berlin Conference in May 2022. Left to right: Art Gertel, Sam Hamilton, Alison McIntosh, and Margaret Bray.**

summary of results in the given timeframe, it should be submitted as soon as possible thereafter. In such cases, the protocol must specify when the results are going to be submitted, together with a justification for the delay.

In short, it is wise to recognise that implications for the protocol and the clinical trial application in CTIS may have downstream granular impact on the ICF and/or the CSR, and may require some head-scratching in terms of process development and template considerations because the medical writing-owned document outputs are complex, interrelated, and should be considered a continuum.

In highlighting these points, I'd also like to point you to the lovely green banner showcasing the value of **The CORE Reference Project**. Not only is CORE Reference the 'go to' resource for authoring CTR-compliant CSRs because the resource is globally applicable, but the

ongoing continual professional development aspect ensures that anything impacting CSRs and public disclosure of CSRs that you need to know, for both ICH and regional jurisdictions, is brought to you in "real time" Choose whether to receive alerts direct to your inbox (sign up at: <https://www.core-reference.org/subscribe>), or to periodically check the News Summary page of the website (<https://www.core-reference.org/news-summaries/>) where the information is archived monthly. After 6 years since the launch of CORE Reference, I am delighted to have assistance from a small but perfectly-formed committee (see banner for details). Together, we will readily maintain the due diligence needed to keep the information that you have come to expect flowing. A selection of the most relevant information in the world of Regulatory Public Disclosure (RPD) since the start of 2022 is below. Enjoy!

Kind regards  
**Sam**

## EMA News

### CTR 536/2014 and CTIS

The EU Clinical Trial Regulation 536/2014 (<https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>) is in force, together with the platform that gives a single-entry point for clinical trials conducted under the Regulation – the EU Clinical Trials Information System (CTIS) – which is now live. If you missed the January 31, 2022 launch, check out the press briefing at <https://www.ema.europa.eu/en/events/joint-press-briefing-clinical-trial-regulation-enters-application-eu>. In the early days of CTIS this page provides updates and links to useful reference materials and is updated regularly as CTIS develops:

<https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system/development-clinical-trials-information-system>. The "CTIS Newsflash" articles appear regularly and can all be accessed at the end of the page. The learning curve is bound to be steep in these early days so the January 2022 minutes from a DIA MW Community meeting that include responses from EMA to questions submitted by this group on CTR/CTIS, are useful and can be viewed here: <https://www.core-reference.org/news-summaries/january-2022/>. The CTIS training Programme Guide is an excellent resource, regularly updated: [https://www.ema.europa.eu/en/documents/other/guide-ctis-training-material-catalogue\\_en.pdf](https://www.ema.europa.eu/en/documents/other/guide-ctis-training-material-catalogue_en.pdf)

Note that Module 13 in the Guide is "Clinical Study Reports submission". It is also helpful to have the 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)" which is open for consultation until Sept 2022. In short, processes and best practice under Policy 0070 are echoed for CTIS: <https://www.ema.europa.eu/en/documents/other/draft-guidance-document>

## [how-approach-protection-personal-data-commercially-confidential-information\\_en.pdf](#)

For those of us supporting investigator-led trials, EMA's support initiatives to help universities and hospitals to navigate CTIS should be passed onto our academic colleagues: <https://www.transparimed.org/single-post/ctis-training-support>

On March 31, 2022, the first Clinical Trial Authorisation (CTA) was issued through CTIS ([https://euclinicaltrials.eu/view-clinical-trial?p\\_p\\_id=emactview\\_WAR\\_emactpublicportlet&p\\_p\\_lifecycle=0&p\\_p\\_state=normal&p\\_p\\_mode=view&p\\_p\\_col\\_id=column-1&p\\_p\\_col\\_count=1&\\_emactview\\_WAR\\_emactpublicportlet\\_number=2022-500137-89-00&\\_emactview\\_WAR\\_emactpublicportlet\\_facesViewIdRender=%2FWEB-INF%2Fviews%2Fview%2Ftabs%2Fsummary.xhtml](https://euclinicaltrials.eu/view-clinical-trial?p_p_id=emactview_WAR_emactpublicportlet&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_emactview_WAR_emactpublicportlet_number=2022-500137-89-00&_emactview_WAR_emactpublicportlet_facesViewIdRender=%2FWEB-INF%2Fviews%2Fview%2Ftabs%2Fsummary.xhtml)). This trial was originally registered under the Directive and in EudraCT, but has been moved under the CTR and into CTIS.

As medical writers take on the challenge of writing "Plain Language Summaries (PLS)" (also known as "lay summaries") mandated by EU CTR 536/201, we will need to assimilate process and procedural knowledge, and to this end a survey has been devised to help better understand trends in PLS, which can be taken here: <https://www.surveymonkey.com/r/PLS-Survey-DIA>. The eventual aim when the survey results are published is to aid with benchmarking your process against your peers.

## DARWIN EU

In February 2022, EMA established the Coordination Centre for the Data Analysis and Real World Interrogation Network (DARWIN EU®): <https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu>. On February 24, a webinar was held to introduce the initiative and highlight opportunities for collaboration, and can be viewed here: [https://www.ema.europa.eu/en/documents/presentation/presentation-darwin-eu-multi-stakeholder-information-webinar\\_en.pdf](https://www.ema.europa.eu/en/documents/presentation/presentation-darwin-eu-multi-stakeholder-information-webinar_en.pdf)

EMA are publishing a quarterly progress update on the work of the HMA-EMA Big Data Steering Group titled "Big Data Highlights". An article in the first issue titled "Regulatory capability to analyse data: pilot on raw data use" is of particular relevance: <https://www.ema.europa.eu/en/documents/newsletter/big-data->

## [highlights-issue-1\\_en.pdf](#)

"EMA, in partnership with the Advisory Group on Raw Data comprising representatives of the Big Data Steering Group, NCAs, EMA committees, and working parties and patients' representatives, is preparing a pilot to clarify the benefits and practicalities of access to individual (raw) patient data from clinical trials in the assessment of medicines. The pilot, which is expected to start in the second quarter of 2022, will analyse raw data from selected marketing authorisation applications to support the CHMP assessment. The results of the pilot, expected in 2023, will help the EU medicines regulatory network to make an informed decision on the place of raw data in regulatory decision-making".

## UK MHRA

In January 2022, the MHRA set out the UK legislative proposals for clinical trials; the consultation period closed on March 14, 2022. Some proposed changes to definitions that include replacing the term "subject" with "participant", updating the definitions of "clinical study" and "clinical trial" and adding "low intervention clinical trial", per the EU CTR are of interest. The term "substantial amendment", however, will be retained in contrast to the new EU CTR change of the term to "substantial modification". The full proposals can be viewed here: <https://www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials/proposals-for-legislative-changes-for-clinical-trials>.

As MHRA gets into its stride as a medicines regulator, we see the drive towards clinical trial transparency and patient centricity, akin to other jurisdictions including the EU, through policy development and initiatives. These guiding principles hold true for the UK as we see with the multi-agency "MakeItPublic" initiative <https://www.hra.nhs.uk/planning-and-improving-research/best-practice/public-involvement/putting-people-first-embedding-public-involvement-health-and-social-care-research/> explained by the Head of Policy and Engagement at the National Health Service (NHS) here: <https://www.hra.nhs.uk/about-us/news-updates/making-transparency-happen-blog-dr-naho-yamazaki-head-policy-and-engage-ment/> and an initiative to boost clinical trial reporting that is working well already: <https://www.transparimed.org/single-post/mhra-hra-isrctn>. The MHRA GCP Inspectorate Blog (sign up for direct alerts to your

inbox here: <https://mhrainspectorate.blog.gov.uk/subscribe/>) helps Sponsors understand what the Regulator has been finding and expects during its inspections. So overall, the UK vision appears clear and so far, the policies and initiatives seem to be supporting that vision.

## FDA Guidance and News

FDA has produced guidances in 2022 that continue to speak to improved real-world applicability for trial results: [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations?utm\\_medium=email&utm\\_source=govdelivery](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations?utm_medium=email&utm_source=govdelivery) and improved patient centricity in drug development: [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients?utm\\_medium=email&utm\\_source=govdelivery](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients?utm_medium=email&utm_source=govdelivery)

The collection and analysis of population pharmacokinetics (PK) data is included in early phase clinical trials and is used to guide drug development and inform recommendations on therapeutic individualisation. The new final guidance on this topic was released in February 2022: [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/population-pharmacokinetics?utm\\_medium=email&utm\\_source=govdelivery](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/population-pharmacokinetics?utm_medium=email&utm_source=govdelivery).

Draft FDA Guidance titled: "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" is open for comment. Per the Introduction: "Adequate representation of these populations in clinical trials and studies supporting regulatory submissions helps ensure that the data generated in the development program reflect the racial and ethnic diversity of the population expected to use the medical product if approved..." Read the guidance in full at: <https://www.fda.gov/media/157635/download>.

These and other guidances can be viewed at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/>.

NIH's Final Policy, effective January 2025, will mandate data management planning and public sharing of clinical trial data for NIH funded studies: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html#:~:text=October%202022%202020-,January%202025%2C%202023,-Related%20Announcements>.

## COVID-19

The COVID-19 pandemic presented multiple challenges, not least to global regulators as all stakeholders learned together. Some of these challenges are well summarised in a 3-part blog in which MHRA inspectors share their experiences dealing with clinical trials during the pandemic, looking at the initial response: <https://mhrainspectorate.blog.gov.uk/2022/02/08/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-1-our-initial-response/>; what has been learned: <https://mhrainspectorate.blog.gov.uk/2022/02/14/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-2-what-we-have-learned/>; and exploring the challenges ahead for clinical trials: <https://mhrainspectorate.blog.gov.uk/2022/02/18/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-3-looking-forward/>

A JAMA survey conducted in July 2021 and published in February 2022 (<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789176>) shows that a representative cohort of US adults overwhelmingly support greater transparency at the FDA. It is suggested that the results may reflect the public's improved understanding of the drug development process in the context of the COVID-19 health emergency. A *Lancet Infectious Diseases* article titled "COVID-19 kick-starts a new era for clinical trials and pandemic preparedness in Europe", shows European regulators calling for "structures and partnerships to enable clinical research and identify regulatory hurdles among the challenges for clinical trials": [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(22\)00061-5/fulltext?dgcid=raven\\_jbs\\_etoc\\_emailhttps://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(22\)00061-5/fulltext?dgcid=raven\\_jbs\\_etoc\\_email](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00061-5/fulltext?dgcid=raven_jbs_etoc_emailhttps://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00061-5/fulltext?dgcid=raven_jbs_etoc_email). The determination to learn from the pandemic and to adapt regulatory pathways and frameworks is clear. On March 30, 2022, EMA showed they

mean exactly that by making this statement "Sponsors can adjust the way they run clinical trials that have been affected by the war in Ukraine using the experience gained during the COVID-19 pandemic. They can also apply the approaches and flexibilities agreed in the context of the pandemic." Read more here: <https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines>

FDA Guidance "Emergency Use Authorization for Vaccines to Prevent COVID-19" was updated on March 31, 2022, superseding the May 21 Guidance: [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19?utm\\_medium=email&utm\\_source=govdelivery](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19?utm_medium=email&utm_source=govdelivery).

## Transparency and Disclosure Resources

As we move to improve transparency in scientific research generally, and more specifically in clinical trials, several initiatives have taken shape in 2022. The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) team have updated and published reporting guidance for health economic evaluations simultaneously in 16 journals including in the September 2021 issue of *Medical Writing* Sept 2021, and on the updated CHEERS 2022 checklist (March 2022): <https://pubmed.ncbi.nlm.nih.gov/35007499/>

The UK is proposing a global effort to strengthen clinical trial transparency. The UK's draft resolution requests that WHO develop a global action plan for implementing the suggested principles at the 76th World Health Assembly in 2023. This is one to keep an eye on.

An article in *The Journal of Law, Medicine & Ethics* titled "Transparency of Regulatory Data across the European Medicines Agency, Health Canada, and US Food and Drug Administration"

provides a snapshot of current clinical trial information sharing by regulators - for a broader audience than just clinical trials professionals. It is actually a really good introduction to the topic for newer members of the medical writing community too: <https://www.cambridge.org/core/journals/journal-of-law-medicine-and-ethics/article/transparency-of-regulatory-data-across-the-european-medicines-agency-health-canada-and-us-food-and-drug-administration/FFD09EC615E261AEFE3E8AE88A268CBA>.

## Patient Centricity

This 2021 CISCRP study highlights clinical trial participant's insights and perceptions: <https://www.openpharma.blog/blog/disclosure/perceptions-and-insights-on-clinical-trial-participation-results-from-the-2021-ciscrp-study/>. We see that the pandemic has improved perceptions around research and improved trust and understanding. Regulators are taking patient **centricity increasingly** seriously and ICH leaders intend to bring patient perspectives into guidelines development: <https://pink.pharmaintelligence.informa.com/PS145721/ICH-Leadership-Aims-To-Bring-Patient-Perspectives-Into-Global-Guideline-Development-Process>.

That's all for this issue. Happy reading.

*With thanks to Margaret Bray  
for editorial support.*

## RPD Special Interest Group (RPD SIG) News

EMWA's Regulatory Public Disclosure (RPD) Special Interest Group (SIG) "Meet and Share" (held on January 27, 2022) recording and PDF are published on the RPD

SIG page of the EMWA website (<https://www.emwa.org/sigs/regulatory-public-disclosure-sig/>). We are greatly saddened by the loss of our colleague Amanda Hunn, who so generously

shared her experience and knowledge on Plain Language Summaries. The video is shared to honour Amanda's memory and with the kind permission of her family.

# Getting Your Foot in the Door

SECTION EDITOR



Ivana Turek  
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## Editorial

*“Pharmacists can only work in pharmacy”.* **False!** Prior to my studies in pharmacy, I thought so until I had an introductory course at the university and heard about many career opportunities after completing a diploma. Still,

the lecturers stressed that at least 95% of pharmacists work in pharmacy and that it is not common for them to work elsewhere. Virginia Chachati had a similar experience and found her new career path in challenging times. Her calmness, devotion, and courage opened a door

to medical writing and she realised her heart’s desire just as Zen Master Dogan Zenji said: *“When both body and mind are at peace, all things appear as they are: perfect, complete, lacking nothing.”*

Ivana

## From pharmacist to medical writer

### A pandemic level catalyst

**P**icture this: you just got married, signed your first mortgage contract, and started a new job. Your husband has an amazing opportunity to work abroad, and you’re going with him. The plan is to move in summer. The next thing you know, a pandemic hits.

This is the story of the fast-paced life changing decisions, wins, and losses, that shaped me into the medical writer I am today.

### Choosing family over work

My journey started in 2019, when there was talk of a new virus that was about to plunge the world into uncertainty. I had started my new job as a pharmacy manager in January 2020. Three months later, lockdown hit in March.

My heart was torn between protecting my loved ones and doing my day job. You see, my husband has type 1 diabetes and my father, over 70, has a heart condition. The panic and fear in the community became overwhelming while I was working at the pharmacy. I felt unprotected and vulnerable, forcing me to quit my job in April.

I switched to working part time as a locum pharmacist (a freelance or temporary pharmacist, where I work at different pharmacies on short term contracts) to reduce my overall exposure to COVID 19. I also started packing, in preparation for moving house from London to Germany in July, 2020.

### Writing my way out

While working part time as a locum pharmacist from April 2020, I got interested in educating people about health online. At the same time, we started to pack as the COVID 19 lockdown

started to lift for the summer. I set my sights on getting out of being a locum pharmacist and looking for a job I could do from anywhere with an internet connection. This was with a view to working remotely to reduce my risk even further – and to avoid having to wear a mask for more than 10 hours a day, which was the most uncomfortable part of working as a locum pharmacist.

I needed a job that I could do in Germany as, although my Master of Pharmacy degree was valid, I couldn’t be a pharmacist there without speaking German up to B2 level (which would take up to 2 years to learn and is considered a high level of fluency). After a lot of research, writing and creating health content drew me in. I could make use of my knowledge and experience as a pharmacist and maintain my registration with the GPhC (which is a professional register for pharmacists and the equivalent of the GMC – the register for doctors). After all, it took 4 years to complete a Master’s degree, then 1 year of training and a registration exam to become a pharmacist. The idea of reaching more people with helpful health knowledge excited me.

### The steep learning curve

To get started, I decided to create my own blog website. This gave me a platform to learn both the structure of a website and a space to practise my writing. I was also inspired by healthcare professionals on YouTube and wanted to get

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involved with creating videos. I learned to write scripts and I taught myself search engine optimisation (SEO) using online resources. At this point I had a lot on my plate.

The learning curve became even steeper as I became a landlady! I had looked into using a property management company to look after our flat in London, and decided the expense was too

much. So I took on the task of learning the laws and regulations around renting out our one-bed flat. I knew I would have to dedicate a lot of time to understand them fully.

But in July 2020, it was time for the big move abroad. We had put down a deposit on an unfurnished flat to rent in Germany. We slept on the floor on our first night as we waited for the furniture to be delivered the next day. Our first days were spent building furniture and learning about the shops and amenities

nearby. After one week, my husband started his new job as a teacher in an international school, and I returned to the UK. This was a truly challenging time for us to separate as we were both undertaking new life experiences. I then spent 5 months continuing to work part time as

**My biggest piece of advice to anyone wanting to get into medical writing is to never give up. This is a journey into new territory and you must have confidence in your skills and your knowledge.**



a locum pharmacist and learning property management. I managed to secure a tenant by November 2020 and luckily got back to Germany that same month, before the Christmas lockdown.

#### Winning and losing

As my confidence grew during my learning, I entered a competition to become a script writer for a pharmacist channel on YouTube. I won! I beat 900 other UK registered pharmacists, validating my growth as a writer. By November, I was back in Germany with a new tenant, a new job, and a world of opportunity.

It felt as though the wins were rolling in; on my flight back to Germany, I met the son of the CEO of a nutrition company. After a great conversation, he linked me with their UK team to create a video for their brand. Unfortunately, this was where my first loss occurred as I agreed to work with no contract and only a promise of payment. The worst outcome came true as my hard work was never remunerated.

But I didn't lose motivation; each challenge was simply a lesson and the next chance was not far off. An online pharmacy contacted me to read

over and edit some pages for their website. Although I was wiser about payment, I made the new mistake of undervaluing my work. To keep myself going, I focused on the portfolio of work I was building and my internet presence growing. I knew it would all be worth it in the end; I just had to believe in the learning-process and keep pushing.

To supplement my income in Germany, I worked part time at my husband's school from December 2020. I was creating lessons for grade 3 to grade 10 as a science teacher and in charge of COVID 19 testing at the school. My portfolio was huge at this point, and I loved the variety of writing I was creating.

#### The power of SEO

I started to get serious about breaking into medical writing when my temporary contract at the school was going to end in June 2021. So I jumped onto LinkedIn and started to flesh out my profile. I rewrote my CV and I started applying to jobs like I had nothing to lose with little success.

I finally caught the eye of a recruiter looking to fill a position at a healthcare agency. I was so

anxious at this point as the end of my paid work with the school was rapidly approaching. I was scared it was just going to be another rejection, it felt like I was trying to find the impossible – a job in the UK where I can work from home in Germany. I once again had to push past these feelings of low self-esteem and just go for it.

#### My foot in the door

The healthcare agency contacted me for an interview! It only took until May 2021, almost 18 months after my journey began, I had finally gotten my foot in the door! I was super relieved and felt so blessed at that moment in time. It had been such a hard year and I was ready to be a full-time medical writer.

I officially started work in July 2021 as a senior content manager and medical copywriter. I learnt how to communicate with clients, train writers, and manage a team. This was on top of working with everyone remotely and learning how to navigate software I hadn't used before. It seemed that I had reached the first plateau of my learning curve and the rest is history.

#### Moral of the story

My biggest piece of advice to anyone wanting to get into medical writing is to never give up. This is a journey into new territory and you must have confidence in your skills and your knowledge. Relish the challenge and keep on pushing until you get where you want to be.

Keep networking and remember to be kind to yourself. Good luck!

#### Acknowledgements

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#### Disclaimers

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

#### Author information

Virginia Chachati, MPharm, has been a UK pharmacist and a medical writer since 2020. She is currently working as a freelance medical writer and social media consultant. She is passionate about helping others get into medical writing, and making the switch from academia or patient-facing clinical roles to flexible remote working.

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# Regulatory Matters

## SECTION EDITORS



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## Editorial

Two years into the pandemic outbreak, our lives have changed one way or another. The pandemic not only has impacted our lifestyle, it might also have impacted our career at some level. We might find ourselves needing to venture out onto new paths, or to explore new areas within the existing paths. In this issue, we are pleased to have our first piece by Tiago Silva who talks about exploring regulatory writing for medical devices from the perspective of a

pharmaceutical regulatory medical writer. Tiago assures us that despite the core differences between the pharmaceutical and medical devices worlds, venturing into a medical device project may not be as daunting as we fear, as we already possess the necessary transferable skills that will get us through the process more easily.

The regulatory landscape of medical devices has continued to evolve during the pandemic. A new EU medical device regulation (MDR) has been fully implemented within the EU since May

2021. How is Switzerland, which is not part of the EU despite its central location in the continent, coping with the changes as a result of the new regulation? Our second piece by Joan D'souza throws some light on the Swiss medical device regulations from the Swiss Medical Devices Act to the conduct of clinical trials for medical devices in the country.

We hope you enjoy reading and derive useful insights from these articles.

**Zuo Yen Lee and Clare Chang**

## From pharmaceuticals to medical devices: What are the transferable skills regulatory medical writers can rely on?

**F**or several years, I have been a regulatory medical writer working with pharmaceutical medicines. Medical devices, however, is a field in which I have no experience. What would happen then, if suddenly a medical device document landed on my lap, along with all the regulatory timelines and constraints regulatory medical writers are all too familiar with? This certainly would not be an easy task, as many differences separate the two worlds. Fortunately, medical writers are used to finding creative solutions for all sorts of challenges on a routine basis. There are several skills an experienced pharmaceutical regulatory medical writer can transfer to developing a medical device document, even without much prior experience in this field.

### Differences between pharmaceuticals and medical devices

The main differences between these two industries are briefly summarised below, pointing out some key topics that pharmaceutical medical writers may want to research before venturing on a medical device project.

### Concepts and terminology

Medical devices have specific concepts, definitions,

and terminology. This includes the actual names of the regulatory documents that, although similar in scope to their pharmaceutical counterparts, have a different designation. Provided below are a few examples:

- Clinical investigation vs. clinical trial or study
- Clinical investigation plan (CIP) vs. clinical study protocol
- Clinical investigation report (CIR) vs. clinical study report (CSR)
- Clinical evaluation report vs. clinical overview and clinical summary (Modules 2.5 and 2.7 of the Common Technical Document)

More specific medical device terminology and concepts are discussed in the previous publications of Doerr et al. (2017)<sup>1</sup> and Billiones and Thomas (2019).<sup>2</sup>

### Type of product, clinical development, and studies performed

According to the Medical Device Regulation 2017/745/EU,<sup>3</sup> medical devices are defined as any kind of instrument, apparatus, appliance, software, implant, reagent, material, or other article used for specific medical purposes that do not achieve the principal intended action by pharmacological, immunological, or metabolic

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means, but which may be assisted in its function by such means. Naturally, being a different type of product compared to pharmaceutical medicines, their development is also different. Medical devices are conceived by medical and engineering experts to meet an identified clinical need. They are developed into prototypes tested at the bench and animal models and perfected before undergoing clinical investigation. Their clinical development is carried out at a faster pace and using smaller sample sizes than that for pharmaceutical medicines, which relies on a lengthier and more specific clinical development process through Phase I-IV clinical trials. The publication by Doerr et al. (2017)<sup>1</sup> further elaborates the main differences between the clinical development of pharmaceutical medicines and medical devices.

### Regulations and guidance

Medical device development is governed by different regulations than pharmaceutical

medicines. In the EU, the Medical Device Regulation 2017/745<sup>3</sup> is the main regulatory reference for these products. This regulation “harmonises the rules for the placing on the market and putting into service of medical devices and their accessories on the Union market [...] sets high standards of quality and safety for medical devices by ensuring, among other things, that data generated in clinical investigations are reliable and robust and that the safety of the subjects participating in a clinical investigation is protected”. In other words, it states the requirements on the clinical development, marketing application, and post-marketing surveillance of medical devices (except for *in vitro* diagnostic medical devices, covered in the *In Vitro* Diagnostic Medical Device Regulation 2017/746).<sup>4</sup>

One key guidance is the international standard ISO 14155:2020,<sup>5</sup> which establishes recommendations for the design, conduct, recording, and reporting of clinical investigations in human subjects using medical devices. This guidance also provides the template structures for key documents, such as the CIP, Investigator’s Brochure, and CIR.

Another important reference is the MEDDEV 2.7/1 revision 4,<sup>6</sup> which establishes the main recommendations in the EU for the clinical evaluation of medical devices, including the development of the clinical evaluation report — the equivalent to Modules 2.5 and 2.7 of the Common Technical Document for pharmaceutical medicines.

The union of pharmaceutical medicines and medical devices produces combination/drug-device products (i.e., products that combine medicines, devices, and/or biological products).

Examples of combination products include pre-filled syringes or pens, corticosteroid inhalers, drug-eluting stents, and transdermal patches. According to the Medical Device Regulation 2017/745,<sup>3</sup> combination products are regulated either under this regulation or under Directive 2001/83/EC of the European Parliament and the Council, and “the two legislative acts should ensure appropriate interaction in terms of consultations during the pre-market assessment, and of exchange of information in the context of vigilance activities involving such combination products”. When developing a combination product, both pharmaceutical and medical device regulations may need to be followed, and this should be addressed on a case-by-case basis.<sup>7</sup>

### Transferable skills from the pharmaceutical to medical devices industry

#### Scientific knowledge and research skills

As a medical writer in an agency environment, I work with different pharmaceutical sponsors, indications, medicines, and regulations. It is not uncommon to start a new project on an indication or medicine that I know little about at first. Moreover, regulatory deadlines are often challenging, leaving writers little time to catch up with the scientific context of the project, which is necessary to tell an accurate and cohesive story in their document. Being able to quickly absorb and appraise new scientific information and

adapt to ever-changing realities is a core medical writing skill that is useful in both pharmaceutical and medical device industries.

Take the example of the combination product ABILIFY MYCITE® (Otsuka Pharmaceutical Co., Ltd/Proteus Digital Health), an aripiprazole tablet embedded with an ingestible sensor to measure medication compliance. If tasked with writing a CIR for it, I would divide my research into 2 components:

Being able to quickly absorb and appraise new scientific information and adapt to ever-changing realities is a core medical writing skill which is useful in both pharmaceutical and medical device industries

- The pharmaceutical component (aripiprazole), which would be more familiar to me: the science behind the product, its development history, and the rationale behind this investigation.
- The technological component (ingestible event marker sensor) would require more research about the specific technological language and concepts. By applying the transferable skills in scientific research, synthesis, and critical appraisal, I could get familiar with this technology more efficiently and understand how this component works together with aripiprazole.

#### Knowledge of regulations, document templates, and guidance

A strong understanding of the International Council for Harmonisation (ICH) recommendations and applicable pharmaceutical regulations is required for medical writers working in the pharmaceutical industry. As stated above, most documents in the pharmaceutical



industry have their counterparts in the medical device industry that, despite some differences, have similarities in scope and even structure. This means that the writing of medical devices regulatory documents may not be as obscure as many medical writers who are used to working with pharmaceutical medicines might assume.

Say, for example, that I have been tasked to write a CIR for an investigation aimed primarily at comparing aripiprazole compliance with ABILIFY MYCITE® versus aripiprazole tablets alone in patients with schizophrenia and no detailed template or example CIR has been provided to me. Although I have never written a CIR before, I have written several CSRs for pharmaceutical medicines. I am familiar with the ICH E3<sup>8</sup> guideline and the CORE Reference.<sup>9</sup> Comparing the ICH E3 or CORE Reference with Annex D of the ISO 14155:2020

“...The writing of medical devices regulatory documents may not be as obscure as many medical writers who are used to work with pharmaceutical medicines might assume.”

(Table 1), a few things are noticeable:

- The ISO 14155:2020 is not as structured and detailed as its pharmaceutical counterparts, allowing for a more flexible approach, and
- The main sections (level 1 headings) are fairly similar. Using my CSR experience, I could plan the structure of the CIR and what to write in each section of the CIR, including writing important sub-headings, defining the level of detail in the text and the cross-references to other sections or external documents, deciding what important tables or figures to include, which source documents to use, and what to ask the subject matter experts.

For example:

- Section 6.1 of the CIR serves a similar purpose to Section 9.4 of the CSR, identifying the characteristics of aripiprazole and the

device component of ABILIFY MYCITE®.

- Section 6.2 of the CIR could include information similar to that in Sections 8 and 9 (excluding Section 9.4) of the CSR. The objectives, endpoints, assessments, and overall study design could be summarised using the ICH E3/CORE Reference as a structural reference.
- The ISO 14155:2020 only designates Section 7 for the investigation results. The ICH E3/CORE Reference could be used as a structural reference for level 2 and 3 sub-headings summarising the disposition of study subjects, results of the primary endpoints, secondary efficacy, safety, and other endpoints.

#### Project management and team leadership

As for pharmaceutical medicines, the development of medical device regulatory documents is part of a product development program that has its own timeline. They are also developed in a cross-functional environment, requiring regular discussion with and coordination of subject

**Table 1. Structure of a clinical study report (CSR) based on the CORE Reference Version 1.0 versus clinical investigation report (CIR) based on ISO 14155:2020**

#### CORE Reference: clinical study report (CSR)

<b>1 Title Page</b>	<b>10 Study Subjects</b>
<b>2 Synopsis</b>	10.1 Disposition of subjects
<b>3 Table of contents</b>	10.2 Protocol deviations
<b>4 List of abbreviations</b>	10.3 Data sets analysed
<b>5 Ethics</b>	10.4 Demographic and other baseline characteristics
5.1 IEC/IRB	10.5 Measurements of treatment compliance
5.2 Ethical conduct of the study	10.6 Extent of exposure
5.3 Subject information and consent	<b>11 Efficacy and other evaluations</b>
<b>6 Investigators and study administrative structure</b>	11.1 Efficacy results
<b>7 Introduction</b>	11.2 Results of statistical issues encountered during the analysis
<b>8 Study objectives and endpoints</b>	11.3 PK, PD, and other analyses results
8.1 Objectives	11.4 Efficacy results summary
8.2 Endpoints	<b>12 Safety evaluation</b>
<b>9 Investigational plan</b>	12.1 AEs
9.1 Overall design and plan	12.2 Analysis of deaths, other SAEs, and other clinically meaningful AEs
9.2 Discussion of study design, including the choice of control groups	12.3 Clinical laboratory evaluation
9.3 Selection of study population	12.4 Vital signs, physical examinations, and other observations related to safety
9.4 Treatment	12.5 Safety results summary
9.5 Efficacy and safety variables	<b>13 Discussion and overall conclusions</b>
9.6 Data quality assurance	<b>14 Tables and figures</b>
9.7 Statistical analysis methods planned in the protocol and determination of sample size	<b>15 Reference list</b>
9.8 Changes in the conduct of the study or planned analyses	<b>16 Appendices</b>



matter experts. Experienced pharmaceutical medical writers are used to running these projects like running a tight ship and are experienced in developing trusting relationships with the team, establishing roles and communication routes, and managing expectations. These skills are transferable to the medical device industry. For writing a CIR, the following could be proposed to the team from the start:

- Timeline: based on drafting, reviewing, approval, and publishing steps
- Data collection plan: based on source documents (CIP, statistical analysis plan, Investigator's Brochure), communication plan and route with subject matter experts' input, and identification of other sources. This also includes compiling and appraising information, identifying potential inconsistencies/conflicts, and proactively working toward their resolution.
- Meeting plan: kick-off meeting to present the project and align roles and expectations, data interpretation meeting to discuss the results and key messages of the investigation, and

comment resolution meetings to address outstanding cross-functional comments.

### Technical writing skills

The objective, precise, lean, and unambiguous writing style used in pharmaceutical regulatory writing should also be applied in writing for medical devices. Pharmaceutical medical writers can transfer their technical writing skills to these new documents, keeping in mind the different terminology, ISO 14155:2020 recommendations for document structure, and applicable style guides.

### Conclusion

There are significant core differences between the pharmaceutical and medical device industries that will require some level of adjustment by regulatory medical writers if they are to move from one to the other. Thankfully, our profession is one used to changes at a fast pace, whether in regulatory or technological settings or by working with different therapeutic areas and treatments. Experienced pharmaceutical medical writers will always find some common ground and make use of their pharmaceutical-acquired skills to smoothly transition to this parallel (but hopefully, not too strange) world.

### Acknowledgements

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### 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.

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### ISO 14155:2020 Annex D: clinical investigation report (CIR)

1	General
2	Cover page
3	Table of contents
4	Summary
5	Introduction
6	Investigational device and methods
6.1	Investigational device description
6.2	Clinical investigation plan
7	Results
8	Discussion and overall conclusions
9	Abbreviated terms and definitions
10	Ethics
11	Investigators and administrative structure of clinical investigation
12	Signature page
13	Annexes to the report

#### Abbreviations:

AE, adverse event; CORE, Clarity and Openness in Reporting: E3-based; CSR, clinical study report; IEC, Independent Ethics Committee; IRB, Institutional Review Board; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event.

### Author information

**Tiago Silva, MSc**, has over 10 years of regulatory medical writing experience in the pharmaceutical industry. He is also the current vice president of the executive committee of the Portuguese Medical Writers Association.

# Swiss medical device regulations

## Introduction

In Switzerland, medical devices are controlled by various regulations; however, there is only one competent authority, Swissmedic, responsible for administering these regulations.<sup>1</sup> Some of the key regulations are presented in Table 1. A few recent changes in Swiss medical device regulations are discussed in this article.

As the world advanced, so did medical device regulations. The year 2021 was a historical year for medical device industries all over the EU. Switzerland is outside of the EU and not part of the common market in Europe; so, what implications did these changes have on the medical device industry in Switzerland? On May 26, 2021, the EU implemented new Medical Device Regulations (MDR); however, Swissmedic lacks official access to the central European medical device database (EUDAMED 3) required by the MDR due to the lack of an updated Mutual Recognition Agreement (MRA). What is the MRA? Since June 1, 2002, Switzerland has regulated medical devices with the EU through the MRA, which deals with all trading of goods, including medical devices.<sup>1</sup>

EUDAMED 3 has been available since December 1, 2020 across Europe. EUDAMED 3 coordinates medical device information across the EU and thus increases transparency.<sup>2</sup> The EU

is prepared to negotiate with Switzerland over transitional provisions in the MRA related to MDR because the EU delegation represents Switzerland's interests in the International Medical Device Regulators Forum (IMDRF). Unfortunately, no agreement has been reached concerning the MRA, and consequently, Switzerland has implemented its own regulations under the revised Swiss Medical Devices Act.

## Swissmedic requirements

According to the revised Swiss Medical Devices Act, the manufacturer must either have a registered place of business in Switzerland or appoint a natural and legal person domiciled in Switzerland to act as the company's representative. A Swiss authorised representative must be designated within specified times for specific devices (Table 2).<sup>3</sup>

In addition to designating an authorised person in Switzerland, the manufacturer must also have designated Swiss residents for three roles: one person responsible for regulatory compliance (PRRC); a distributor responsible for ensuring the device's availability in the Swiss market; and an importer responsible for placing the device from a foreign country onto the Swiss market.<sup>3</sup> Each delegated representative has a fiduciary responsibility to the manufacturer and the Swiss authority to align with the mandate

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and, if required, terminate the mandate if the manufacturer acts contrary to the mandate. The manufacturer has the option of submitting the technical documentation file of the new medical device directly to Swissmedic upon contractual agreement with the authorised representative instead of keeping with the authorised representative. Nonetheless, most authorised representatives request the technical file from their manufacturers.

## Clinical trials

Switzerland mandates human clinical trials for specific medical devices. The procedure for approval of a clinical trial for medical devices will depend upon the category of the clinical trial. These procedures are listed by category below:

- Category A clinical trials /post-market trials: The devices used in this clinical trial have the CE label, and the devices used in this trial are used as stated in the CE-labelled instructions. Clinical trials falling under this category must be submitted only to the ethics committee.
- Category C clinical trials /pre-market trials: The devices used in this clinical trial either do

Table 1. Swiss regulations

Description	Regulation	Reference
The Act guarantees safe and effective therapeutic products including medical devices.	The Federal Law (IDRAC 174478) on Therapeutic Products and Medical Devices (812.21)	Ch. 1, Art. 1 ; and Ch. 3.
The enforced ordinance provides all provisions related to medical devices. It forms the legal basis for placing medical devices in Switzerland.	Medical Devices Ordinance of Jul-01-2020 (IDRAC 315597)(MedDO)(812.213).	Ch.1, Ch. 2, Ch. 3, and Ch. 5.
The Act governs all requirements including ethics when human beings are involved in research.	The Federal Act (IDRAC 175144) on Research Involving Human Beings (810.30).	Ch.1, Sect.1, Art.1.
This ordinance regulates medical devices with respect to the conduct, procedure, duties, and responsibilities of the research ethics committee, and the registration of their clinical trials in accordance with the Article 1 Medical Devices ordinance of July 1, 2020.	The Ordinance (IDRAC 315596) on Clinical Trials for Medical Devices (ClinO-MD) (812.213.3). (German)	Art. 1.
This ordinance regulates the conduct, procedure, duties, and responsibilities of the research ethics committee, and the registration of the clinical trials.	The Ordinance (IDRAC 174400) on Clinical Trials in Human Research (ClinO)(810.305).	Ch.1, Sect.1, Art.1; and Ch.2, Sect. 1, Art. 20.



Illustration: Chris Monk www.yellowduck.net

not have the CE label, are not used per the CE-labelled instructions, or are prohibited in Switzerland. Clinical trials falling under this category must be submitted to both the ethics committee and to the Swissmedic.<sup>4</sup>

Before commencing the medical device clinical trial, it is essential to obtain the permission of both: (1) the cantonal ethics committee and (2) the Swissmedic, as well as to submit the trial on the ethics committee portal (“Basec”) and the Swissmedic portal (“eMessage”).<sup>4</sup> It is also critical that submissions on both the portals are made on the same day. As per the rules implemented on May 26, 2021, Swissmedic will authorise only those trials that the ethics committee has approved. Once the submission has been made on both the portals, the complete document will be reviewed in 38 days.<sup>4</sup> The manufacturer or its authorised representative must submit technical documentation to initiate a clinical investigation of a medical device.

**Registration process**

Furthermore, according to the new regulations, before placing the medical device on the market, all new medical devices must be registered

through the Swissmedic and receive a CE label through a designated body.<sup>3</sup> The manufacturer, authorised person, or importer must register the device on the Swissmedic within 30 days of introducing the device in the Swiss market. Once the medical device is registered through the Swissmedic, the device obtains a unique device identification number (UDI). The Swiss Single Registration Number (CHRN) is a unique identification number that the Swissmedic assigns to Swiss manufacturers, authorised representatives, and importers upon request.<sup>3</sup> The CHRN number must be obtained within 3 months of placing the device on the market.<sup>3</sup> The CHRN improves the traceability of the device and enables ease of identification of the device. Once the MRA is updated, the process will change, and the manufacturers will receive their unique identification numbers through the EUDAMED 3.

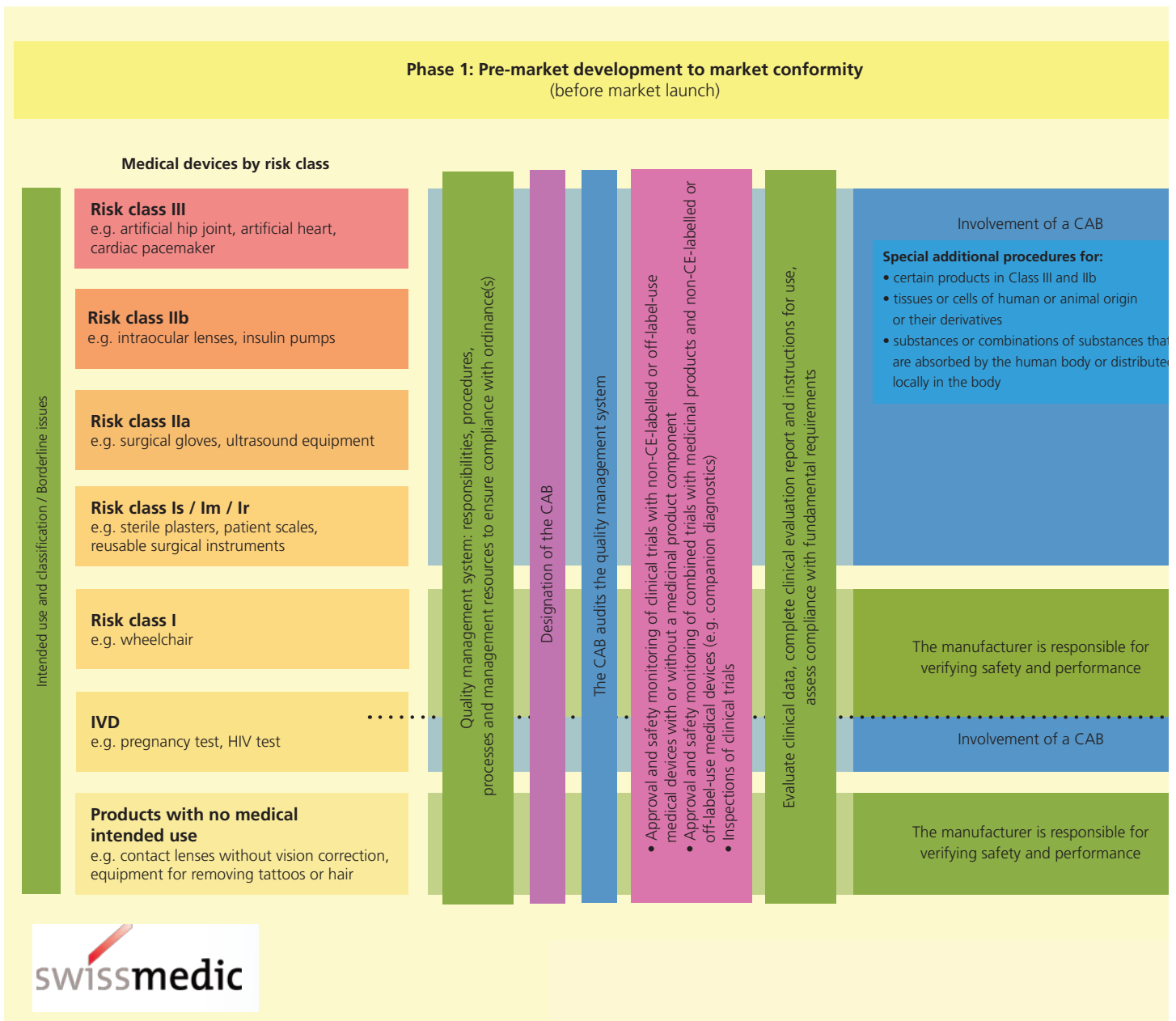
**Conformity assessment standard**

Once the medical device is registered through the Swissmedic, the device must meet the conformity assessment standards before the device is placed in the Swiss market.<sup>3</sup> The conformity standards are evaluated by a list of private

entities or designated bodies. Devices certified by notified bodies in a member state of the EU or the European Economic Area are equivalent to those certified by a Swiss notified body. The timelines for approval/clearance/certification of a product by a designated body will depend on the complexity of the medical device. Generally, the timeline for Class IIa/IIb categories will be 4 to 12 months, with a follow-up review within 3 years.<sup>3</sup> Swissmedic must complete its clinical investigation in 60 days. Medical device compliance is attained once the device receives its CE label. The CE label on the medical device permits free transactions of the medical devices across the EU market. The device is ready for placement in the Swiss and EU markets upon receipt of its CE label/certificate. The CE label is valid for five years but may be extended several times.<sup>3</sup> Swissmedic is continuously involved in the conformity assessment of medical devices by reviewing the documents issued by the designated bodies, auditing these bodies, and publishing the annual surveillance report of the audits on the Swissmedic website each year. The identification number of the designated body is placed beside its CE label.

**Table 2. Timelines to designate a Swiss authorised representative**

Medical devices	Class	Designation of a Swiss authorised representative by:
High-risk devices	Class III, IIb implantable, and active implantable medical devices.	December 31, 2021
Moderate-risk devices	Non-implantable Class IIb and Class IIa.	March 31, 2022
Low-risk devices	Class I.	July 31, 2022
Systems and procedure packs		July 31, 2022



**Figure 1. The tasks of Swissmedic – lifecycle of a medical device**

The following are the designated bodies authorised to issue CE labels:

- The SQS (NB 1250) is the local Swiss designated body for issuing the CE label. CE labels issued under the old Medical Devices Ordinance (oMedDO) dated October 17, 2001 became void as of May 26, 2021. This means no new certificates can be issued under the oMedDO. However, certificates already issued under oMedDO will remain valid until their expiry date or until May 26, 2024.
- The Nando website offers a list of foreign notified bodies.<sup>3</sup>

### Inspections

Swissmedic is responsible for continuous inspections of authorised representatives, importers, and manufacturers. Cantons carry out their inspections across multiple nursing homes and clinics, and the Swissmedic conduct relevant inspections in the hospitals. Foreign governmental inspections of medical devices are permitted in Switzerland provided the foreign body notifies the Swissmedic of its inspection at least 30 days before the planned inspection, receives a prior agreement of the company on the scope and the extent of inspection, and delivers a copy of the inspection within ten days after

issuing the report.<sup>5</sup> If there are problems with the medical devices, it is mandatory for those first placing the medical device on the Swiss market to recall the device. The manufacturer also has an obligation to report to Swissmedic the measures they undertook to resolve the problem.

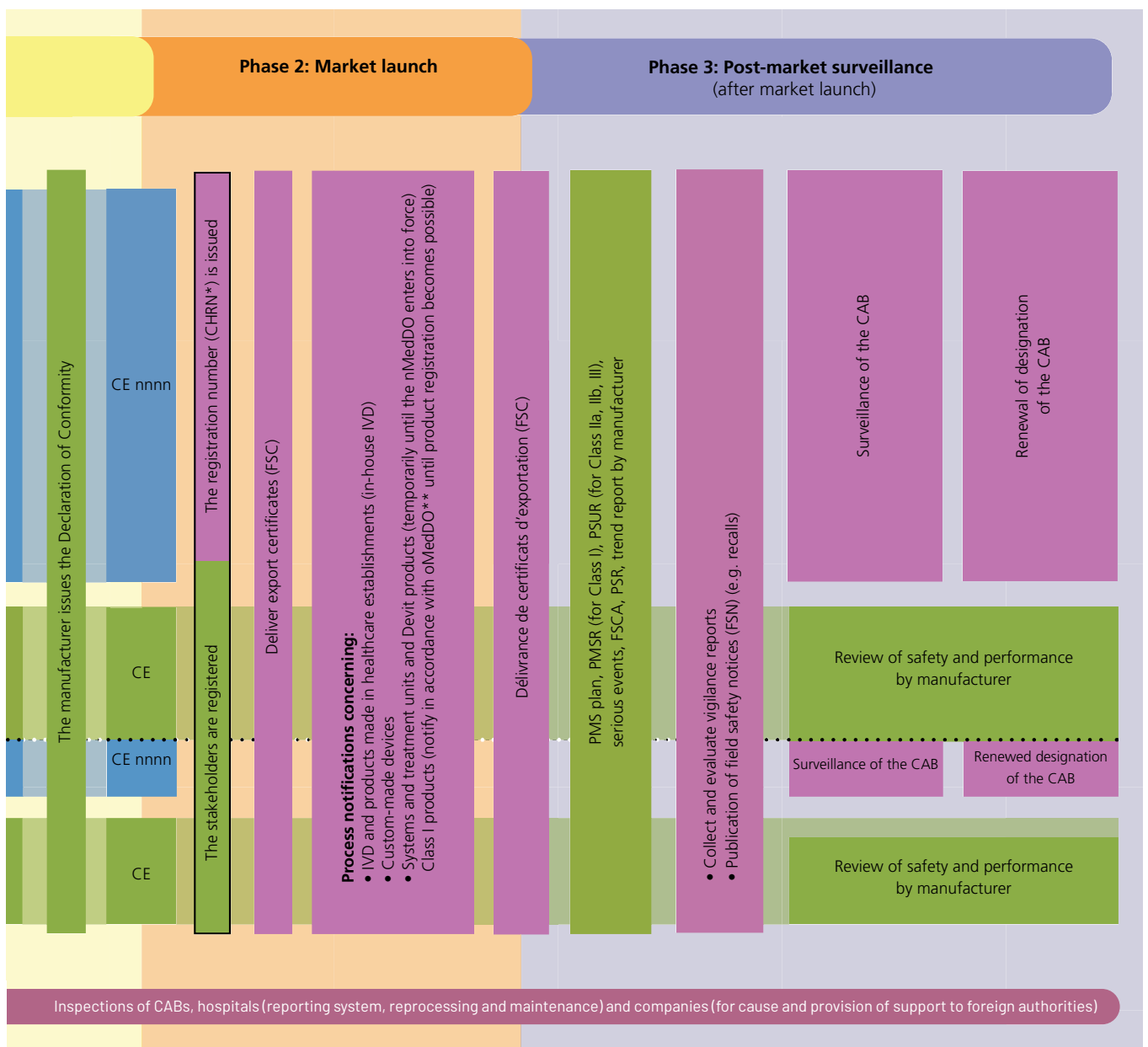
### Conclusion

For now, Switzerland has worked its way through and looks forward to an updated MRA between Switzerland and the EU.

### Disclosures and conflicts of interest

The author declares no conflict of interests.

The different stakeholders in the process: ● CAB / designated body ● Swissmedic ● Manufacturer



\*CHRN = Swiss Single Registration Number. \*\*Medical Devices Ordinance of 17 October 2001 (version of 1 August 2020)

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# Veterinary Medical Writing

## SECTION EDITORS



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### Editorial

For this issue of Veterinary Medical Writing, we have two articles from the veterinary world. The first is about the niche but increasingly in-demand service of veterinary public relations (PR). For decades, the veterinary profession has enjoyed a privileged position in society and has been (and still is!) valued by the general public. However, the profession is increasingly facing challenges to its reputation, affecting individual practices and the profession as a whole. Through the rise of social media, which gives everyone an equal platform at its egalitarian best, any individual with a grudge can inflict quite serious reputational damage to practice with a few clicks of a mouse. Drawing on her experience in veterinary PR, Caroline Chambers gives an overview of how veterinary Businesses can overcome any harmful social

media exposure and proactively build a large, positive social media presence in their community.

Elsewhere, the 2021 Autumn EMWA conference was not only the scene of the first hybrid conference, it also witnessed the first veterinary workshop on the subject of One Health. A topic that has a reputation for being abstract, intangible and something that vets do, Elissa Burnside provides a witness statement from this inaugural workshop, led by Kilian Unger. Regular readers will know that we here at Veterinary Medical Writing are big cheerleaders for One Health, and, as Elissa testifies, the new workshop is a valuable addition to the EMWA CE canon. The only thing to ask now is this; if medics look after human health and vets are in charge of animal health, which profession is the custodian of environmental health?

Finally, where the geopolitical outlook has become so much darker since the last issue of MEW, we at Veterinary Medical Writing section pay tribute to the veterinary profession's response to the crisis in Ukraine by high-lighting the VetsforUkraine initiative in the latest issue of FTHM. An example of veterinary leaders stepping up to assist colleagues caught up in this awful conflict and provide practical support for the animal welfare and public health challenges that will inevitably arise from it.

Finally, we at Veterinary Medical Writing say a fond farewell to Jennifer Bell, who has departed as co-editor to focus on the MEW Biotechnology section. All we can say is their gain is our loss and we thank her for her input and wish her all the best.

Louisa Marcombes

## Embracing a new era: The growing role of PR and social media in vet practice

The way we gain information and form opinions about businesses has fundamentally changed in the last two decades. Gone are the days when word of mouth held sway, and now we carry around an ever-updating hotbed of public opinion in our pockets. This has impacted all business sectors in terms of reputation management and communications, and the veterinary profession is no exception. We are seeing a growing role for veterinary public relations (PR) and a greater focus on digital activities and social media. This sphere is not without its challenges, though, and this article discusses the changing environment and considers how practices can harness communications to reap positive rewards.

### The challenges of our interconnected world

With the digital era in full swing, communications between businesses and their clients are now quicker and easier, but they can also be more reactive and confrontational. Social platforms

give the opportunity to vent frustrations in an instant, and the normalisation of this in our culture means that the expectations of courtesy we hold for in-person interactions do not always apply. This raises huge challenges for veterinary professionals, who deal with complex and difficult situations every day in which emotions can very understandably run high. Despite a veterinary team's best efforts, commitment, and dedication, outcomes are not always positive, and the ultimate fear is a social media storm – with the story potentially being picked up by mainstream media journalists and amplified further.

There is no denying the basis of these fears; indeed, the situation can be professionally damaging and emotionally exhausting, and particularly frustrating when practices are inhibited from telling their side of the story since it would be inappropriate to comment on the specifics of a case in the public domain. However, the era of instant communication is also full of opportunity, and there is much that veterinary

Caroline Chambers

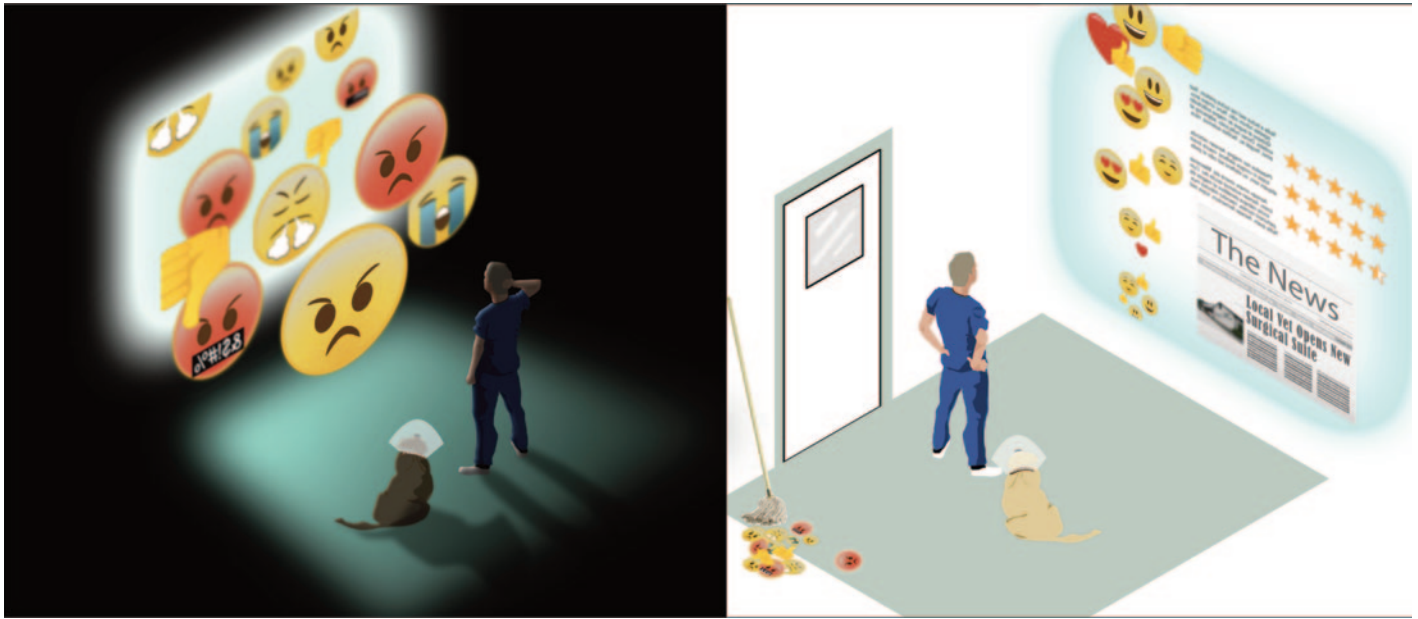
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practices can gain from this interconnected world. In order to keep the risks in perspective and experience the benefits, practices need to go beyond this reactive mindset and take a proactive approach to communications.

### A proactive approach

A proactive approach involves utilising media communications to build up a positive "bank" of good reputation, such that the impact of any negative publicity is ameliorated and seen in context. This positive PR activity will build on the good work of the practice and amplify its strong reputation amongst satisfied clients. Indeed, in some social media storms around vet practices, it is heartening to see that it is other



Graphic: Louisa Marcombes

clients who leap to the defence of their beloved practice. Of course, client loyalty develops primarily from people's personal interactions with the business rather than media communications, but a well-managed PR strategy will strengthen this by reinforcing the practice's image.

Outside the social sphere, building up a good reputation with local press can also pay dividends. If a practice has positive relationships with local journalists and editors, publications may be less inclined to pick up negative stories about them, or may get in touch with staff to request a more balanced view rather than printing the story without question.

As well as avoiding negative publicity, attention to PR can bring many other benefits to veterinary practices. These include business advantages through attracting new clients and retaining current clients, as well as recruitment benefits via showcasing the ethos of the team and encouraging applications from prospective staff. Current staff can also reap the rewards, as their work-life will be more fulfilling if they are proud to be part of a very well-regarded practice, and this can help boost retention. Taken together, all these benefits are significant and will be particularly welcome in a challenging time for veterinary practices, with the fallout from the pandemic adding to the well-recognised industry pressures in terms of wellbeing, understaffing,

and burnout.

**The era of instant communication is also full of opportunity, and there is much that veterinary practices can gain from this interconnected world.**

Given these benefits, a growing number of veterinary practices are beginning to give a greater emphasis to PR. Some larger practices or groups may have a defined marketing manager, while smaller independent practices often share the responsibilities amongst the team.

### **Leveraging press relationships**

When it comes to developing a media communications strategy for a veterinary practice, there is a lot to consider as PR encompasses a wide range of activities with print and digital media. Considering print media initially, it is generally most beneficial for veterinary practices to develop good relationships with local press.

Sharing positive stories about the practice with local publications – for example, sending out press releases about any expansion of the service or facilities or staff members receiving awards – helps raise the practice's profile with current and prospective clients. Featuring in the press builds up the business's credibility and helps practices set themselves up as the local voice of advice for pet-related matters.

Local, feel-good stories tend to be popular amongst readers, so press contacts will appreciate being supplied with these stories, and this can lay the foundation for long-lasting and mutually beneficial relationships. Veterinary practices can also build on these relationships by inviting local press contacts along to any events they organise, such as open days and charity fundraisers.

Some practices, particularly larger or referral businesses, can also benefit from engaging with the veterinary press. Publishing stories in this sector-specific media can help raise the profile of the practice as well as individual vets within it.

### **Social media**

Social media, while raising significant challenges for the veterinary sector, also provides a wealth of opportunities. The conversational nature of these platforms supports relationship building, helping veterinary teams establish a rapport with

clients on a much wider scale than can be achieved in-house on a normal day. Many pet owners love to share pictures and stories of their pets on social media, and veterinary teams can invest in client relationships by encouraging these positive interactions, possibly introducing fun activities such as photo competitions if they have the time. Social platforms also allow practices to showcase the

personable side of the business, helping to reinforce their approachable and caring image –

**Being featuring in the press builds up the business's credibility, and helps practices set themselves up as the local voice of advice for pet-related matters.**

which in turn helps avoid negative publicity, as people are less likely to attack a business when they see the human face.

Practices can also use social media to reinforce pet care messages, firstly by answering client questions and secondly by crafting posts to highlight the value of preventative treatments, routine check-ups, and perhaps the practice's healthcare plan. These posts can help boost business at the same time as improving pet care, extending the reach of team-client interactions beyond the physical premises.

In terms of which platforms practices focus on, Facebook is by far still the most popular. Instagram and TikTok are also increasingly attractive, perhaps because of the reduced likelihood of engaging in toxic "debates". The "always on" nature of Twitter and the need to engage with the community means it is often too time-intensive for many practices, although veterinary professionals will often use it in a personal capacity but related to professional interests. LinkedIn is also becoming increasingly popular with vets as a means of engaging with other veterinary professionals.

It is worth ensuring that the team member(s)

Social platforms also allow practices to showcase the personable side of the business, helping to reinforce their approachable and caring image.

in charge of social media has training in what makes an effective strategy, as social interactions can take up a lot of time, and the business must gain a return from this investment. Training can also help team members avoid inadvertently triggering any difficult situations and respond in the most appropriate way to settle any issues that may arise.

### The importance of a cohesive strategy

Alongside developing positive press relationships and forming an effective social media plan, there are many other elements to a successful PR strategy for veterinary practices. The practice website will be particularly important in terms of client relations, and other useful avenues for communication with the public include blogs, emailers, leaflets, and so on. For those practices looking to interact with the veterinary profession more broadly, relationships with veterinary media outlets will prove very valuable. The key is to identify which of these elements will be important for the individual practice and then weave them together into a cohesive strategy to meet the business's goals.

Overall, PR for veterinary practices is growing

in importance, but the veterinary sector is very specialised, and it is important to take this context into account when applying general principles of PR. Many practices would welcome training in this regard, but it was only this year that saw the launch of the first educational platform dedicated to educating veterinary professionals on sector-specific PR and marketing (Vetti). In the future, it is likely that more practices will place a greater focus on PR to maintain their reputation and meet their business goals.

### Disclosures and conflicts of interest

The author is employed by Companion Consultancy, which runs the veterinary PR and marketing portal Vetti.

### Author information

**Caroline Chambers** worked as a vet in small animal practice for 6 years before moving into the world of communications. After gaining 18 months' experience in life science marketing and medical writing, she joined Companion Consultancy where she works as a Senior Account Manager and Lead Copywriter.



## From the Horse's Mouth

The quarterly pick of the news from the veterinary world

**I**n response to the war in Ukraine, the Federation of Veterinarians of Europe (FVE) has partnered with the World Veterinary Association and the European Federation of Companion Animal Veterinary Associations to assist Ukrainian veterinarians, their families and animals caught up in the conflict, it was reported on the FVE website on February 25, 2022.

Through a purpose-built web portal, [vetsforukraine.com](http://vetsforukraine.com), Ukrainian veterinarians and their colleagues from the rest of Europe

and beyond can access information and resources to tackle the significant veterinary challenges that have arisen since the start of the crisis on February 24. This hub provides practical advice about housing for refugee veterinarians and addresses the specific needs of Ukrainian veterinary students who have had their studies interrupted. There is guidance on recognising the professional qualifications of Ukrainian veterinarians to support them in finding work whilst in their adoptive countries. Furthermore, there is also practical advice on

the evacuation of pets, farm animals, and zoo animals from Ukraine with update-to-date guidance on disease risk posed by the cross-border movement of a large number of animals. This initiative demonstrates how professional bodies can mobilise to support colleagues caught in a conflict zone and highlights the importance of the logistics of domestic animals at a time of war, not only on the basis of animal welfare but also in terms of food security and public health.



# The first veterinary EMWA workshop: A witness statement

**T**he EMWA November 2021 virtual conference marked an important milestone: the first-ever EMWA veterinary medical writing workshop. At the helm of this workshop was Dr Kilian Unger, a vet with heaps of experience in veterinary public health policy, who undertook the massive task of presenting the One Health topic to a diverse audience of medical writers (from vets to medical translators to regulatory writers). As a part-time veterinary surgeon and full-time regulatory medical writer, I have always been fascinated by the concept of One Health after first hearing about it during my time at university. I was very keen to jump right in and find out what opportunities lay ahead to help change the way we see the world of science, medicine, and ecology.

The structure of the workshop entailed some obligatory pre-workshop reading, and the workshop itself shone a spotlight on the hot topics of the One Health paradigm. Delegates were afterwards invited in their post-workshop assignment to write a short (700-word) essay on one of the presented topics, allowing them a deeper exploration of the themes discussed,

which were later shared with me for the writing of this article.

This article represents a summary of the topics discussed during the workshop and in the essays to give readers a taste of this exciting new veterinary workshop.

## A bit of One Health history

Pre-workshop preparation was with the mandatory reading of a very interesting paper by Evans and Leighton;<sup>1</sup> a bit like journal club prep, to help us understand the basics of the One Health concept.

On the day, the workshop first started with a bit of history; the idea of One Health is nothing new. It can actually be traced back to the great Greek philosophers, including Hippocrates and Aristotle, but gained in popularity from the 19th century onwards.<sup>1</sup> In 1858, Rudolph Virchow, an early proponent of One Health, wrote: “Between animal and human medicine, there are no dividing lines – nor should there be. The object is different, but the experience obtained constitutes the basis of all medicine”.<sup>1</sup> In the mid-20th century, Calvin Schwabe built on this belief

**Elissa Burnside**

Scinopsis Medical Writing

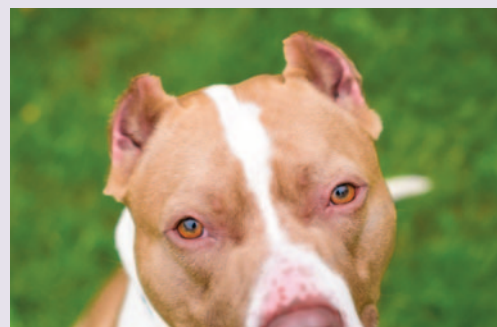
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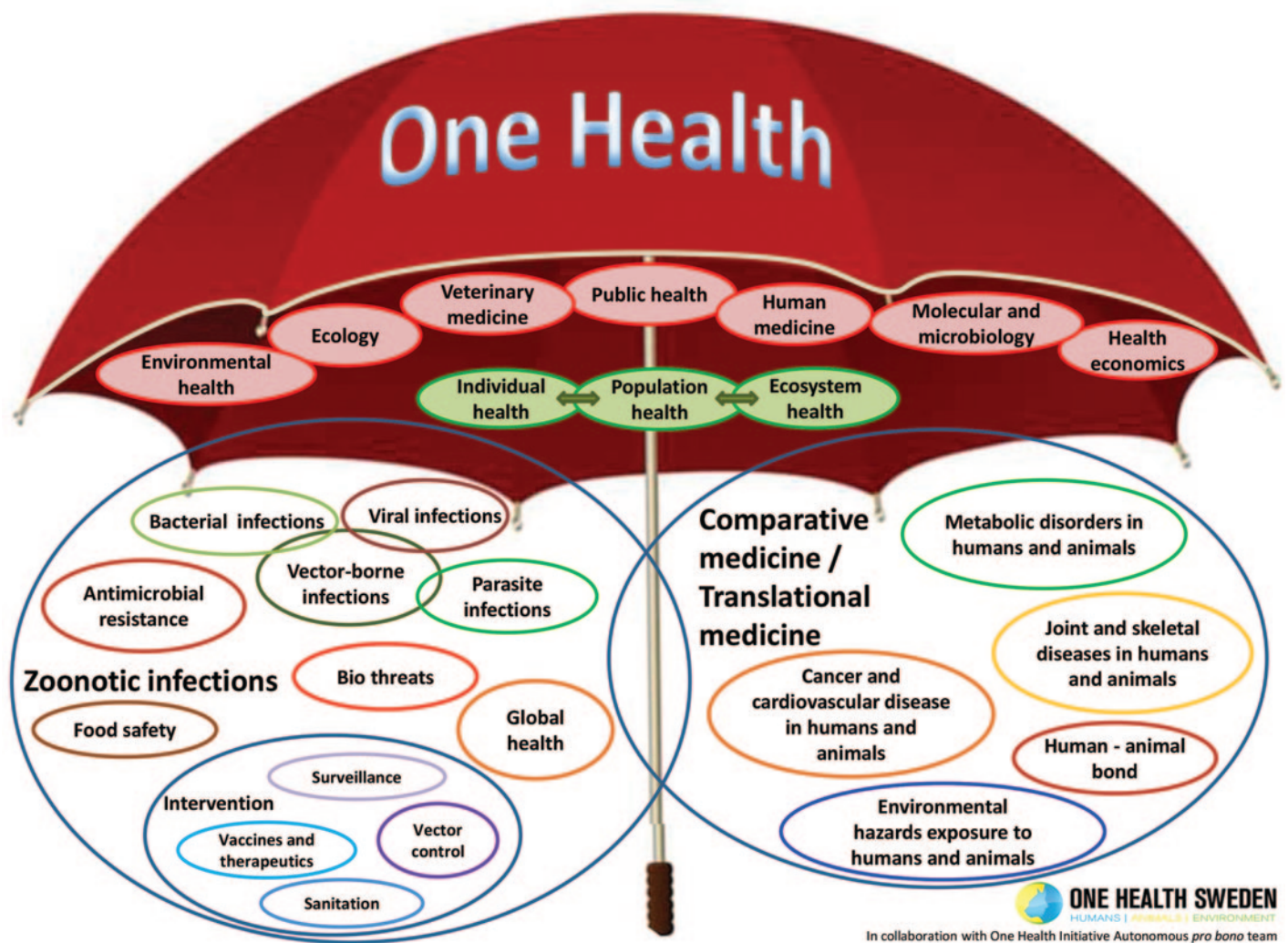
by exploring the interface between veterinary and human medicine and coined the term “One Medicine”.<sup>1</sup> In the early 2000s, the term “One Health” made its first official appearance when emerging zoonotic diseases such as bovine spongiform encephalitis (BSE), severe acute respiratory syndrome (SARS), and avian influenza accelerated the need for collaboration between vets, human doctors, health organisations, and health authorities. In 2007, a “One Health Initiative Task Force” was created in the US, and the “One Health Commission” was established.<sup>2</sup> In 2008, a number of influential organisations (including the WHO, FAO, OIE, UNICEF, and World Bank) developed a “One World, One Health” framework to coordinate medical and veterinary health policies more effectively,<sup>3</sup> and since then a huge network of One Health organisations have cropped up all over the globe.

**A** recent pre-print article has advanced the case for comparative medicine on BioRxiv, the Humanimalhub.com reported on February 14, 2022. The study demonstrated that the molecular basis of many naturally occurring canine tumours have high concordance with the oncogenic drivers in humans. The analysis, involving 28 tumour types from 708 client-owned dogs representing 96 breeds and cross-breeds, identified 50 mutations in established oncogenes and tumour suppressors. Furthermore, the *TP53* gene, which is mutated in about 50% to 60% of human cancers, was mutated in over 30% of canine cases in this study. With the caveat that, at the time of writing, this data is yet to undergo peer-review, it does provide further evidence of the suitability for canine patients to be spontaneous models for human cancers.

**T**he Royal Society for the Protection of Animals (RSPCA) in the UK saw an 86% increase in reports of ear cropping in dogs to its emergency helpline in the last 12 months, it was reported in the *Vet Times* on March 7, 2022. Despite the practice, where a dog’s ears are surgically altered to be pointed and stand erect, being illegal in the UK since 2006, the rise of reported cases since 2015, the year records were first kept, has been exponential. In 2015, 14 reports were filed regarding ear cropping in dogs, by the end of 2021 this had risen to 188, which represents an overall increase of 1,243%. Although this is attributed, in part, due to increased public awareness of the practice, the promotion of dogs with cropped ears on social media and by celebrity influencers is likely to have played a role. It signals a worrying trend



that pet owners are circumventing the ban by importing animals from overseas from regions where the practice is legal, thereby driving up the demand for a procedure that is effectively a cosmetic mutilation and serious animal welfare issue. It is envisaged that legislation to ban the import of dogs who have undergone the procedure into the UK will reverse this trend and the RSPCA are currently campaigning for such legislation to be adopted.



**Figure 1. The One Health umbrella showing the many concepts, fields, and issues included in the idea of One Health**

Source: One Health Sweden and the One Health Initiative pro bono team

So, what exactly is “One Health” today? Well, there’s apparently no universally accepted definition, and some organisations regularly tweak their definition of One Health to keep it up to date.<sup>4</sup> Kilian gave examples of a few definitions, including this one by the CDC: “a collaborative, multisectoral, and transdisciplinary approach – working at the local, regional, national, and global levels – with the goal of achieving optimal health outcomes recognising the interconnection between people, animals, plants, and their shared environment”.<sup>5</sup> A vast and overarching definition I know, but the topic in and of itself is vast and overarching.

### The One Health umbrella

To help summarise One Health, this slightly crowded but comprehensive infographic was introduced to illustrate the different concepts, fields, and issues contained under the One

Health umbrella (Figure 1). This diagram was to form the basis of our post-workshop assignment. The aim was that we each spy out an aspect of One Health that we felt especially passionate about, research all the advantages and drawbacks, and relate it more closely to our world, our sphere of medical writing. I chose the topic of comparative medicine for my post-workshop assignment, one of two out of the seven delegates to do so.

### Comparative medicine

One of the many interesting One Health topics for vets is the potential power of comparative medicine. We’re not talking here about the use of genetically selected (or modified) laboratory animals used in pre-clinical studies (which unfortunately translates into quite a high failure rate for new therapeutics). The focus of comparative medicine here is based on companion

animals and the potential cooperation between vets and the human pharmaceutical industry. Pets and people have similar genetic traits, similar physiologies, and live in the same environment with common stressors. Many human diseases, including cancers and other acute or chronic diseases (such as epilepsy and diabetes mellitus), can also affect dogs and cats. Unfortunately, comparative medicine still has major limitations, including the (currently) quite poor quality of veterinary clinical trials, the sometimes poor predictive power of animal models, and the relatively low funding of veterinary research. (For anyone interested in learning more about comparative medicine, Veterinary Medical Writing editor Louisa Marcombes wrote a great summary article about this in the September 2021 issue of this journal.)<sup>6</sup>

During the workshop, however, a clear enthusiasm from the audience could be felt: the

idea of veterinary clinical trials for human drugs was an exciting new field and finding ways to combat their limitations felt like an exhilarating challenge.

For my post-workshop assignment, I discussed the potential role of medical writers in this new era of comparative medicine, in which we would be the pillars to support the enhanced communication between vets, human doctors, pharmaceutical groups, regulatory bodies, and the general public that the comparative medicine framework demands. In their take on the same subject, the other participant exposed the issue of rare and neglected diseases, showing how research and communication on how these diseases affect animals may help advance potential treatment options for humans. The participant highlighted the shared environmental hazards between humans and animals with the interesting example of podocniosis, a debilitating and stigmatised disease caused by repeated exposure to minerals in irritant volcanic soils, affecting an estimated 4 million people worldwide.<sup>7</sup> The participant speculated that research into how animals, both wild and domesticated, react to these soils might change our view on the currently known pathophysiology and treatment options in humans. The topic was a great start to get our juices flowing!

### Antimicrobial resistance

The next topic explored during the workshop was antimicrobial resistance, a very real and very worrying issue that affects both vets and human doctors on a daily basis. Kilian described this issue in great detail, explaining how microbes can evolve to resist the action of antimicrobial medicines through selection pressure caused by the overuse and misuse of antimicrobials in both the veterinary and human medical sectors. He showed us frightening projections of the number of deaths attributable to antimicrobial resistance in 2050, with a catastrophic estimated 4.7 million deaths per year in Asia (Figure 2).<sup>8</sup> Fortunately, this issue has received a lot of attention in recent years by national governments as well as international organisations (OIE, WHO, FAO, EU commission, etc.), which are setting up global action plans to improve awareness, optimise the use of antimicrobials in both animal and human medicine, improve hygiene standards, and increase investment in new diagnostic and treatment options.<sup>9</sup> A very good One Health challenge.

One workshop participant approached this topic by highlighting the fact that many antimicrobials used today have come from microbes, which have evolved antimicrobials as

a defence mechanism against other microorganisms; antimicrobial resistance is just the microbe's way to keep surviving and avoid extinction. However, we have unwittingly selected for antimicrobial resistance in agriculture and aquaculture by using antimicrobials as growth promoters and increasing the concentrations of heavy metals in the environment.<sup>10</sup> Antimicrobial resistance not only affects human health but also animal health and the food chain, making it vital for doctors and vets to work together. This participant also emphasised that the One Health approach should be taught from a young age, to enable future scientists and the general public to instinctively view Health as a whole, taking into account the impact of the interconnectedness of human, animal, and environmental health, and acting more efficiently and quickly when faced with issues such as antimicrobial resistance. One such initiative, the One Health Lessons project ([www.onehealthlessons.com](http://www.onehealthlessons.com)), aims to do precisely this, and its founder, a veterinarian, is a recent contributor to this journal.<sup>11</sup> Do we not, as medical writers, have the duty to get the word out too?

### Vector-borne and zoonotic diseases

Kilian then illustrated the accelerating trend of zoonotic diseases. These are infectious diseases that can spread from animals to humans and vice versa, and he gave examples of recent human outbreaks of West Nile Fever, transmitted by mosquitoes from infected birds, and Q-fever, transmitted by direct contact with infected goats. The risk of spillover diseases is increasing at an alarming rate, mostly due to changes in land use, urbanisation, global travel, and mass migration. The current emergence of monkeypox in non-endemic countries is a case in point.

Good quality scientific communication with the general public was highlighted by one of the participants as being crucial to fighting these kinds of diseases. She wrote that "it is a daunting task to lay down complex issues in a relatable and accessible way", but emphasised the importance of the One Health approach even on a small scale, by providing the example of malaria, a mosquito-borne disease endemic in many tropical and subtropical countries. Helping people understand the importance of adapting their surrounding environment to prevent such

disease, e.g. by using mosquito nets and not leaving stagnant water nearby, is actually not a straightforward task. But it accentuates the need for appropriate and targeted communication on how the environment can affect human health, be it directly or indirectly.

As another participant highlighted, "the medical writing community bears considerable responsibility for the reliability, accuracy, and even at times, the transparency of data presented to the scientific community and general public". And the COVID-19 pandemic really shone a light on this. This zoonotic disease shook the world of health and health information, with good communication being of paramount importance to help prevent its spread. Misinformation and disinformation about the COVID-19 virus, vaccines, and possible treatments were shown to have caused unnecessary harm and avoidable fatalities.<sup>12</sup>

As the participant put it, the pandemic has "taught humankind valuable lessons in cooperation, information-sharing [...], and the importance of disseminating evidence-based findings".

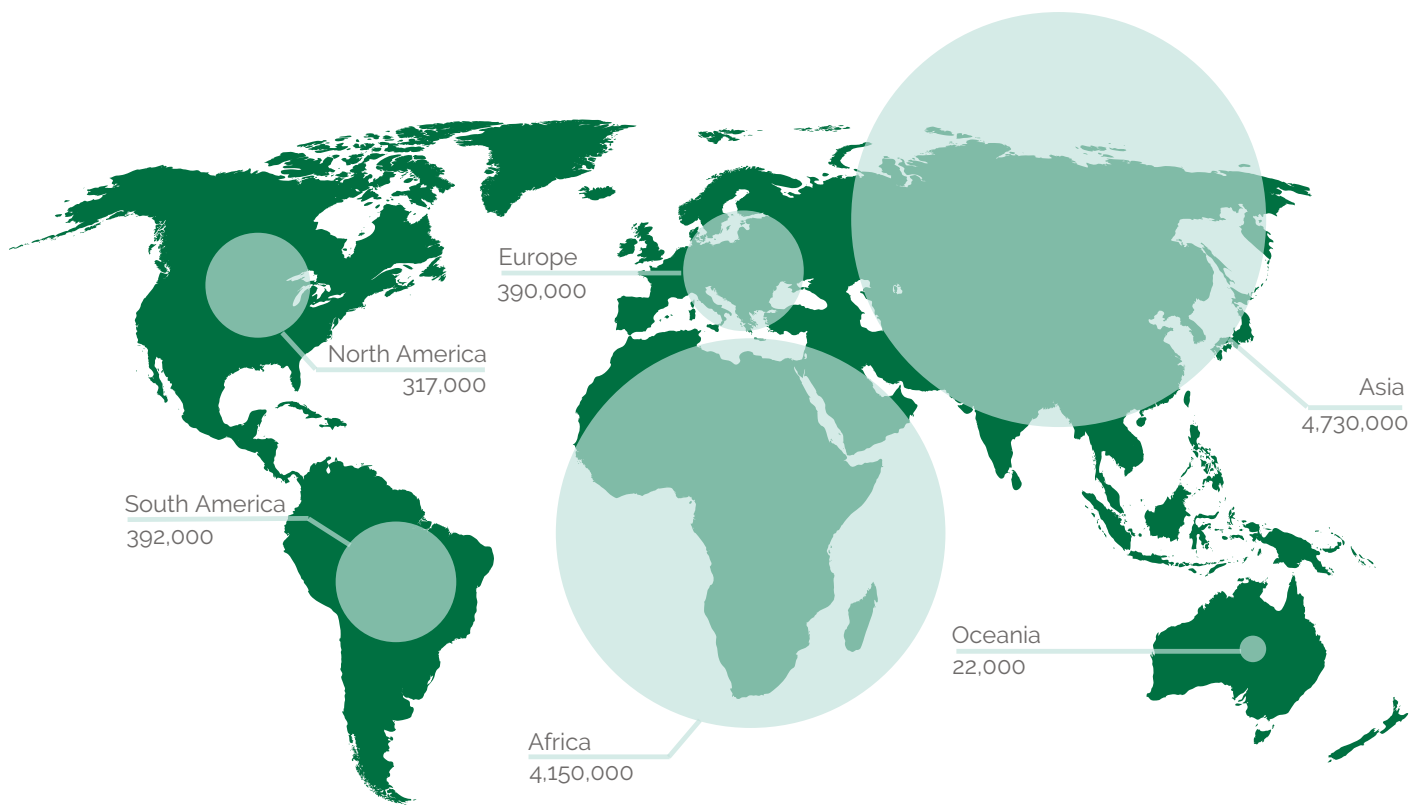
As part of the One Health approach, another participant laid out the skills that vets acquire through their chosen career path. She emphasised, through the example of the COVID-19 pandemic, that "the scientific community, including medical writers, can benefit from an interdisciplinary approach and should be aware of the knowledge that those from an animal health background can bring".

### Food security and food safety

As Kilian noted, epidemics in animals can also have huge effects on human health. The increase in zoonotic diseases in food-producing animals can lead to major issues in food safety. And even animal epidemics with low or zero zoonotic potential, such as foot-and-mouth disease or African swine fever, are equally as frightening, as they can lead to huge economic losses and jeopardise food security for millions of people.

It can be easily understood how a One Health approach to food is vital. Creating an open channel of communication between vets, human doctors, epidemiologists and veterinary pharmaceutical groups can improve both food safety and food security. One participant observed that the One Health approach "can be used to design and implement programmes, policies, and

This zoonotic disease [COVID-19] shook the world of health and health information, with good communication being of paramount importance to help prevent spread.



**Figure 2a. Projected annual deaths attributable to AMR in 2050, broken down to geographic region**

legislation”, “reduce [...] direct and indirect healthcare costs”, and even “reduce the amount of food waste and increase utilisation of nutrients”. However, the participant is fully aware that “One Health brings complexity to food safety management” and that “the food web itself is already complex”. There is still a lot of work to be done.

### So what’s in it for medical writers?

In order to stick to his workshop schedule, Kilian had to repeatedly rein back the passionate discussions from the participants. As one participant put it: “the whole concept of One Health is as vast as the many issues and challenges associated with human, animal and environmental health”. What I see in that sentence is that everyone can find a sense of purpose within it. There are still many unanswered questions on the real-life implementation of the One Health concept, and still much work to be done to incorporate it in all aspects of science and medicine. Facilitating communication between stakeholders and involving the general public may shift the concept

“The whole concept of One Health is as vast as the many issues and challenges associated with human, animal and environmental health.”

of One Health into an everyday, routine way of thinking and seeing the world. And medical writers, as Kilian implied, may have an important role to play in this. This workshop has influenced my prescribing habits as a vet, to think not only about the individual animal I am treating but also about the consequences on the surrounding humans and environment, and it has also transformed my way of researching topics as a medical writer, to take into account the many aspects surrounding human and animal health. This shift to a One Health approach and the increasing funding in veterinary medical care is helping veterinary medical writing gain traction in Europe and globally. I hope that this successful veterinary workshop is the first of many of its kind.

### Acknowledgements

The author would like to thank Kilian Unger for hosting the One Health workshop and Emily Atkinson, Tamara Bar-Magen, Jennifer Bell, Laetitia Paris, Susanne Schmidt-Wussow, and Petal Smart for kindly sharing their post-

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### Disclaimers

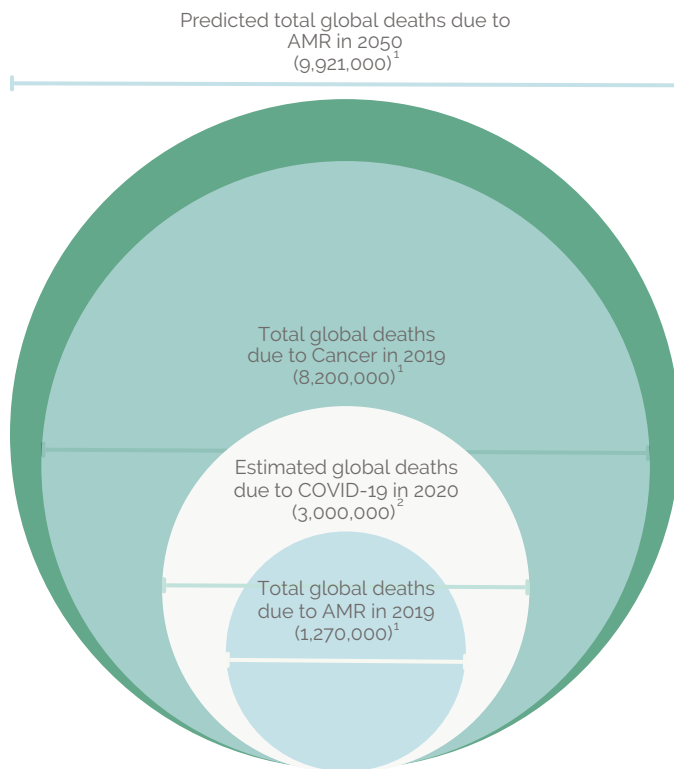
The opinions expressed in this article are the author’s own and not necessarily shared by his employer or EMWA.

### Disclosures and conflicts of interest

The author declares no conflicts of interest.

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**Figure 2b. Quantitative comparator of projected global 2050 AMR death rates with contemporary data for AMR deaths, cancer deaths and COVID-19 deaths.**

AMR = Antimicrobial resistance

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**RESULTS ARE COMING SOON**

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# Lingua Franca and Beyond

## Formatting references – shall we revisit?

In this issue, Yateendra Joshi, ELS (D), is our contributor. Yateen has been copyediting research papers for more than 30 years and has been teaching researchers how to write, publish, and present scientific data for more than 15. He is a member of the European Association of Science Editors (EASE) Council, as well as of the editorial board of *Information Design Journal*. Information design

is of particular interest to Yateen, so no wonder that he brings reference structure and design to our attention. We are familiar with Vancouver referencing style and Harvard style; we know that we need to follow a journal's guidelines, but do we really think of the impact of reference structure on the message transferred? Do we really catch that where a year of publication is placed matters? Do we really consider typographic coding to be of help? These and other questions are considered by

## SECTION EDITOR



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Yateen and it is my pleasure to welcome him as our second EASE guest to the *Lingua Franca and Beyond* section.

Maria

## Formatting of bibliographical references: Elements, sequencing, and typography

One are the days when librarians would photocopy abstracts of research papers, paste the abstracts on index cards, and arrange the cards in the desired sequence for easy retrieval: the issue of the journal itself – the source of the research paper in question – would be on display and eventually end up as part of a bound volume on library shelves. Researchers would retrieve the volume from the shelves if, after reading the abstract, they decided to read the full paper. Now we have search engines, electronic repositories, and the internet – all we need to do is to keep clicking. Nobody in their right minds would suggest that we go back to index cards. And yet, when it comes to listing the bibliographic details of the sources we consulted, under the heading “References”, we seem to be living in the Stone Age.

Yes, there are stray signs of change. For example, the most recent edition of the *AMA Style Manual* no longer recommends that the place of publication be included in a reference giving the bibliographic details of a book.<sup>1</sup> On the other hand, many journals now require that digital object identifiers (DOIs) be given for papers published in journals. But what I'd like to do in this article is to argue that we rethink the matter of how to present bibliographic references: what items to include in a typical entry or record or reference, in what

sequence to arrange them, and how to format them typographically. This leaves out punctuation – the marks used to separate the various items or elements or parts of a reference – because I have aired my grievance elsewhere, so to speak.<sup>2</sup>

The discussion that follows is based on the premise that such references lists are processed not by machines alone but are used by people – and not only to locate a particular source but *also to peruse the list as a whole*, just as they would scan a table of contents.

Should we present  
John Arthur Brown  
as Brown J A or  
Brown, JA or  
Brown, J. A. or  
John, Arthur B. . . .?

### The elements or parts of a bibliographic reference

The elements that make up a reference differ depending on the nature of the source, which may be a paper in a journal, a chapter from a multi-authored book, an entire book, a conference presentation, a web

page, and so on. Nearly all, however, have one or more authors and most carry the year of publication (although there's that n.d., for no date). A reference to a paper in a journal, for instance, gives the title of the paper, the name of the journal, usually the journal's volume number and sometimes an issue number, and the page numbers (the first and the last page on which the paper appears). A reference to a multi-authored book will carry the names of the book's editors as well; that to a conference will have the date,

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venue, a theme or title, and the organisers; that to a standard (ISO standard, for example) will have a number; that to a web page will have a URL; and so on.

Each of these elements is informative: the year tells us how recent or old the source is; the title of a paper, what the paper is about; the inclusive page numbers, its length (whether, for example, it is a 1-page note or a detailed treatment of the topic running to many pages).

However, there is one item that hardly has any value and yet takes up space, and ties us into knots when it comes to punctuation: the initials of authors. Do we really need that bit? How likely is it that the initials of authors are the only item that distinguishes one source from another in a reference? So long as we continue to insist on supplying the initials, we also need to agree on how to present them. Should we present John Arthur Brown as Brown J A or Brown, JA or Brown, J. A. or John, Arthur B. . . .? Another argument in favour of dropping the initials is that in the Harvard system of citations (the author-date system) the reference mirrors the citation more closely, because citations seldom carry initials (unless we have the same names in the same sequence with the same year).

Some details of referencing are aimed at saving space, which was certainly an important



consideration in print publications; in the digital world, it is not, and we should rethink the requirements of abbreviating journal titles. Full titles are not only more informative but also allow us to dispense with the mechanics of abbreviating (J or Jnl for Journal, to take a common example) and, yet another trivial point (pun intended), namely should it be Biol or Biol., for example.

### The sequence of elements in a bibliographic reference

The sequence is more or less uniform across publishers except the year of publication: some publishers place it next to the names of authors; others move it closer to the name of the journal and especially its volume number. Given that the volume number of a serial (periodical) is a function of time, the second option seems logical. However, I argue in favour of placing the year after the names of authors because (a) it mirrors the citation in the name–date format; (b) it makes it easier to skim the list of references to note how current – or dated – they are; and (c) it shortens the procession of numbers that typically occurs at the end of a reference to a paper in a journal, comprising the volume number, the issue number where applicable, and the inclusive page numbers – a succession of digits that makes the sequence more prone to errors. For example, compare “Brown. 2020. Sequencing of references. *Imaginary Journal* 7:15–20” and “Brown. Sequencing of references. *Imaginary Journal*, 2020, 7: 15–20”.

### The typography of elements in a bibliographic reference

Lastly, consider the look. After all, computers may scan, extract, parse, re-arrange ... but the literature is there to be read by people, and references are part of the literature. Some people even indulge in a quick scan of the list of references before they start reading the paper itself. And typographic coding helps readers: italics for journal titles and boldface for volume numbers once used to be standard, but the minimalist approach is increasingly doing away with that – a trend that we need to reconsider. I also have one other suggestion that may horrify some: use boldface for titles of articles, chapters, etc., which are the main source; the names of journals and of books, for example, are mere containers. This will facilitate a quick scan of reference lists to take in the scope or the topics of sources that have been used as support for statements or assertions made in the main text. Again, at least in the author–date style, the list of references is sorted alphabetically by the names of authors, making it easier if one is looking for a particular name or names. Placing the year immediately after the names makes it easier if one is looking for how current the references are; so why not introduce boldface for names of articles or chapters to make it easier to scan the list with that variable in mind? And if you are concerned that boldface will make a page look spotty, you can always tone the boldface down a bit (how about 60% black instead of 100%?).

As writers we strive to help readers; as editors, we strive to help both authors and readers. I hope these suggestions are a step in that direction. You may disagree with the details, but is it not time that we revisit our ideas of handling bibliographic references?

### Disclosures and conflicts of interest

The author declares no conflicts of interest.

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# Gained in Translation

## Classical languages: Possible teaching strategies

### SECTION EDITORS



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### Introduction

In the March 2021 edition of *Medical Writing*, this column made a brief journey through the classical roots of medical terminology and showed how this developed in English over the centuries. Medicine was born in ancient Greece, where for the first time diseases began to be seen no longer as the interventions of gods and superhuman forces but as the natural consequence of physical elements within the human body. Patients were visited systematically and meticulously by doctors who started developing their terminology, and this was subsequently taken over by the Romans who partially translated it into Latin. The result was the development of a bilingual Graeco-Latin terminology, with Latin grammar and Greek components, that absorbed some elements from other languages and still survives today.

This terminology is characterised by the use of basic linguistic elements called “combining

forms”: lexical units used to form new words that include elements such as prefixes, roots, and suffixes, put together repeatedly in numerous combinations. In addition to giving the key features of the medical terminology such as richness, uniqueness, expressivity, flexibility, and attitude to composition, they also work as useful memory helpers for doctors. This terminology is truly international in character: it is found in all languages, in what appears to be as an interlanguage convergence of loanwords occurring within a communication network of international size. Consequently, learning medical terminology is particularly important but it is also a challenging task, as the weight of classical education has faded away in schools and universities during the last decades. What to do then? Perhaps, knowing the opinion of some experts might be helpful.

learning medical terminology is particularly important but it is also a challenging task, as the weight of classical education has faded away in schools and universities during the last decades.

reasons for them bringing it back is that until recently the schools that did teach Latin and

Greek were the expensive private institutions; the idea is to do that so that they can be seen as providing an equal level of education.” But is this feasible? According to Petra Zrnkova, medical translator, and former lecturer from the Institute of Foreign Languages of Comenius University in Bratislava, this is indeed feasible. She reports the experience from her own university, where the students get “all background, all the grammars, and linguistic structures [...] in the first year of their study,” in just two semesters.

**Paolo Rega**

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### Medical symbols used today

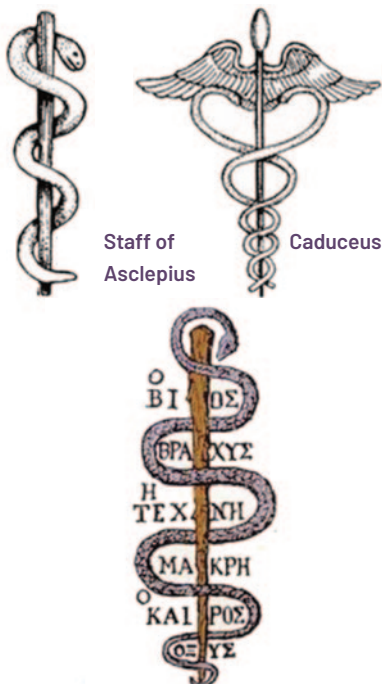


Figure 1: The symbols of medicine: the rod of Asclepius and the caduceus

### Bringing back the study of classical languages

The UK government has already realised the problem and soon will introduce the study of classical languages in state schools.

“I do not know if they see it as a problem”, says Virginia Allum, a registered nurse in Scotland and expert in medical English. “[...] One of the

### Using IT technologies and apps

However, according to Virginia Allum, the task can be feasible if IT technologies and apps are used: “What students can get on their smartphones is much more than what they could get 10 years ago. They expect mobile learning, and to me that would be the way to go: to get some sort of mobile learning they can access when they have time, for 5 minutes a day or whatever, to



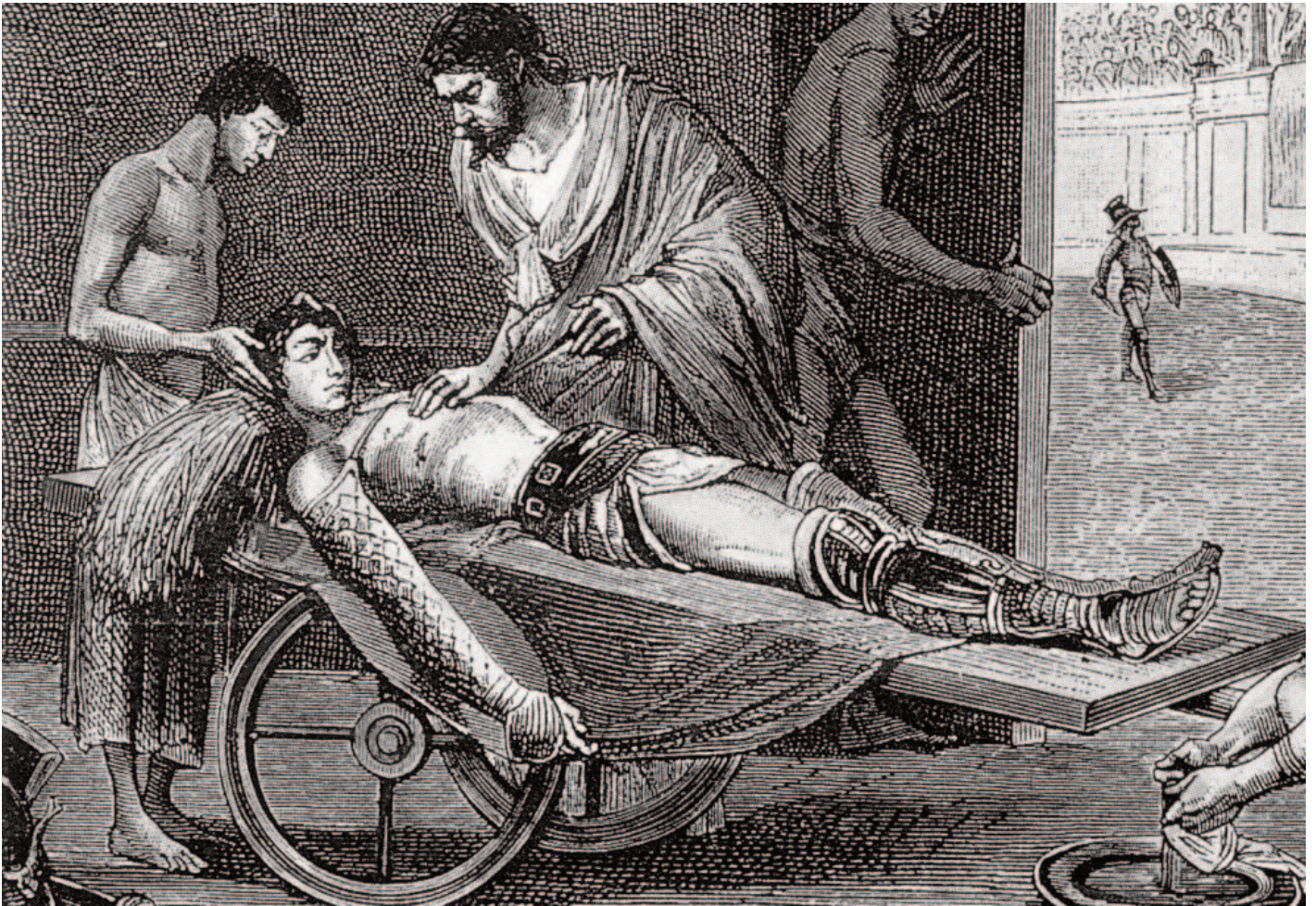
## CLASSICAL STUDIES



GREEK      LATIN

Figure 2: Pictures advertising classical studies on the website of the University of Houston.





learn, practice, and do activities.” One model is Duolingo, the famous American language-learning website and mobile app.

“That would be the model to follow,” said Ms Allum. “And a lot of practice, not getting too heavy into the background of prefixes and suffixes [...] It’s got to be quick, it’s got to be easy, and it’s got to be fun.”

### A lexical study with a practical use

In any case, it is indeed difficult to imagine biology and medical students finding enough time to study the grammar and structures of classical languages, even with the aid of technology, but perhaps this is not necessary. That is the opinion of Giuseppe Germano, Professor of Medieval and Humanistic Latin Literature at the Department of Humanities of the University of Naples Federico II.

“It would be necessary to have a targeted study on the lexicon that focuses on the etymology of scientific words and brings light on the linguistic families they derive from,” said Dr Germano. However, he agrees on developing the classical background starting in high school. “This would

be an essential base, especially because teenagers have higher memory skills and more time at their disposal.” He even has a clear idea of who should be in charge of a possible course: “He should be someone with a classical culture or even a high school teacher, not necessarily a university professor [...] someone who has a good education, with a specific study that focuses on the possible use in the context of medicine, biology, and other related disciplines.”

Therefore, a study of the lexicon seems to be the best direction, especially because it could be accomplished much more easily by students. Emad Rashed Beniamen, Lecturer of Italian at the Department of Italian Studies of the Ain Shams University in Cairo, agrees with Professor Germano.

“I would say that it is not easy to force students to study Greek and Latin grammar,” said Dr Beniamen. “Instead, they might focus their attention on the lexicon and its elements which will help them decipher and understand the scientific names and physiological conditions that appear incomprehensible for those who have no medical background.”

In other words, the study of classical languages can be focused on the lexicon and the processes that govern the composition of scientific terms, with particular attention to the previously mentioned “combining forms.” Professor Beniamen agrees with Professor Germano also on the point of who should be in charge of the teaching.

“I see someone that comes from the world of humanities [...] and knows the Greek and Latin used in the scientific terminology,” he said.

The teacher described should be a person who has studied philology and specialised languages, specifically those used in medicine and biology.

In a society that values practical purposes above all else, the previously described approach would have to be practical, as proven by the personal experience of Professor Beniamen himself.

“As translator and interpreter, I often translate medical records from Arab to Italian and vice versa and from English to Italian,” said Dr Beniamen. “Therefore, knowing and grasping the meaning of these combining forms from the technical/ scientific terminology allows me to

## Medical Terminology

### Combining form/

word root	Meaning
● aden/o	gland
● carcin/o	cancerous; cancer
● -oma	tumor
● angio/o	vessel (blood)
● lymph/a	lymph
● splen/o	spleen
● myel/o	bone marrow
● genesis	producing

**Figure 3: Some combining forms used in medical terminology.**

assimilate and understand a medical report or an information pamphlet and, therefore, to translate it in other languages. It is an approach with very concrete results.”

## Raising awareness

However, memorising a series of words of Latin and Greek origin and seeing how they are used in another language risks reducing everything to a mnemonic dynamic. In this situation, you are facilitated in learning technical lexicon if you have studied classical languages and have a certain proficiency which helps understand how the classical lexicon has developed in the modern languages. This is the opinion of Antonio Rollo, Associate Professor of Byzantine Civilization at the University of Naples “L’Orientale”:

“Probably, the teaching approach is wrong and must be changed. In the current world, where Latin and Greek are seen as ancient relics, we can revive them by showing the great contribution that these ancient languages have given to modern ones. This might be an incentive to get to understand the importance of the study of these languages and how they continue to have weight in the current Western culture.”

In other words, Professor Rollo suggests raising the awareness of this topic among professors and students alike. This can be done with a systematic approach that should no longer be based on literature alone, but also on a path with a technical aspect, which highlights how the Graeco-Latin terminology serves to construct modern languages. In fact, modern languages are studied with literature, by first considering the

In the current world, where Latin and Greek are seen as ancient relics, we can revive them by showing the great contribution that these ancient languages have given to modern ones.

grammar, and subsequently, by reading the books of great authors, whereas teachers never take into consideration the enormous contribution that classical languages have given to the development of technical terminology, something which, to be honest, would be sacrosanct.

“What needs to be done,” continues Professor Rollo, “is to raise the awareness among the members of the teaching staff and push them to organise a teaching programme that gives value to the classical languages in relation to the modern ones. This approach might have a profound meaning, because it would have a very productive educational impact and would show that studying ancient languages does not mean limiting it to the languages themselves, but it means to comprehend the great contribution that ancient languages have given, especially to the development of scientific terminology.”

## Conclusions

It is more and more evident that recovering the teaching of classical languages has become particularly important for all those who practice medical and scientific writing. The point is to find an elegant, practical, and effective strategy that would not hinder the tight schedule common for students of medicine and biology. If the opinions

of the experts interviewed are considered, it is possible to imagine a strategy that can be summed up as follows:

1. Bring back the study of classical languages, not just in universities but also in high schools. Teenagers, in fact, have better memory skills and more time at their disposal;
2. Use mobile learning: this can make the study of classical languages quick, easy, and fun;
3. Focus on the lexicon and the lexical elements known as “combining forms”: they can be employed as useful memory helpers for students and doctors;
4. Employ teachers who are well educated in the ancient languages and have studied specialised languages such as those used in medicine and biology;
5. Raise the awareness of this topic among students and teachers alike, who should become aware of the great contribution made by classical languages to the development of technical and medical terminology, as an important incentive to study and learn it.

In their eagerness to advance science and technology, scientists are perhaps overlooking the importance of medical terminology that, with its richness, effectiveness, and ductility, is a powerful weapon in itself: drawing attention to its study and preservation would be a great advantage for us all.

**Paolo Rega** is a Medical Writer and Translator at Rega Medical Writing Services.



**Figure 4: Mobile learning consists of the use of electronic devices for educational purposes. Mobile learning technologies include handheld computers, MP3 players, notebooks, mobile phones, and tablets.**

# My First Medical Writing

## SECTION EDITOR



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### Editorial

In this issue, I have the pleasure to share an insightful article by Sibyl Bertrand. As a molecular biologist, Sibyl worked in numerous cancer research institutes in France before arriving in the UK where she pursued her PhD in clinical medicine at the University of Oxford,

studying mutagenesis mechanism in cancer predisposition and tumour development. After a quick post-doc, she realised she enjoyed sitting at her computer writing more than at the bench pipetting. So, she recently leapt into medical communications as an associate medical writer.

It was a great pleasure to work with Sibyl in

the creation of this piece, which I hope you enjoy as much as I did. And, if you're an aspiring medical writer eager to gain experience in this field, this space offers you an opportunity to publish your work and start creating your portfolio.

**Evguenia**

## Endometriosis – The monthly workforce loss

**E**ndometriosis is a disease estimated to impact about 10% of reproductive-age women,<sup>1</sup> the equivalent of 190 million women worldwide.<sup>2</sup> It impairs the physical, mental, sexual, and social well-being of affected women. On a broader scale, it translates into a societal burden including productivity loss, lower study activity and grades,<sup>3</sup> and an estimated cost on the healthcare system equivalent to other chronic diseases such as type 2 diabetes or Crohn's disease.<sup>4</sup> Given the features of such disease, one might think that by now, patients would be easily diagnosed, healthcare practitioners would know how to ease their patients' symptoms, and researchers would be close to finding its origin and a cure. Unfortunately, although endometriosis impacts numerous women, its aetiology is still unknown, its diagnosis is still difficult, and its treatment is still palliative, which all together renders this disease a complex challenge for patients, clinicians, and researchers.

But what is endometriosis? Taking its roots from the Greek *endos* (inside), *metra* (womb/uterus), and *-osis* (disease), endometriosis can be translated as a "disease of the uterus"; clinically, it is defined by the presence of endometrium-like tissue outside of the uterus.<sup>5</sup> During each menstrual cycle, the endometrium (the uterus lining, made of epithelium and connective tissues) thickens and sheds under the influence of the two main female hormones: estrogen and

**Unfortunately, although endometriosis impacts numerous women, its aetiology is still unknown, its diagnosis is still difficult, and its treatment is still palliative.**

progesterone. The latter scenario – when the endometrium sheds – is commonly known as a period. In patients suffering from endometriosis, endometrial cells are found in places other than the uterus, such as fallopian tubes or ovaries. Sometimes, endometrial cells even manage to escape the female reproductive system and attach to organs at vicinities such as the bladder or the colon. As mentioned earlier, when a period occurs, the endometrial cells answer the hormonal call and break down – even the endometrial cells located outside of the uterus. So, in endometriosis, the shedding of cells located outside of the uterus will ultimately cause lesions and/or alter the function of the colonised organs. And like any wound one gets, pain accompanies the process.

The origin of endometriosis is still unknown.

One hypothesis suggests that reflux of menstrual debris through the fallopian tubes – also called retrograde menstruation – could disseminate viable endometrial cells outside the uterus.<sup>6</sup> Nevertheless, given that 90% of women experience retrograde menstruation,<sup>7</sup> it is likely that other factors are involved in the development of the disease. Genetic predisposition, prenatal exposure to endocrine-disrupting chemicals, the intestinal and female track microbiome, the immune system, and sex hormones are possible factors.<sup>8</sup>

The diagnosis of endometriosis is a complex challenge, both for patients and healthcare



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practitioners. Indeed, endometriosis is a spectrum disease which means it includes a wide range of signs and symptoms alongside a variety of subtypes and clinical presentations. A non-exhaustive list of most commonly observed symptoms experienced by patients includes:<sup>2</sup>

- painful periods
- pain occurring during and/or after intercourse
- painful bowel movement and/or urination
- fatigue
- infertility

Some women might show no sign or experience no symptoms of the disease; while others can experience painful symptoms and/or infertility,<sup>9</sup> presenting endometrioma (endometrial tissue forming a cyst on the ovary) and/or extra-pelvic lesion.<sup>2</sup> Puzzled with the broad range of symptoms, biomarkers (detected via non-invasive methods such as a blood sample) could help clinicians quickly and easily detect or rule out the diagnosis of endometriosis. Unfortunately, the current gold standard procedure available to diagnose endometriosis combines surgical examination via laparoscopy (a surgical procedure to access the inside of the abdomen) and histological examination of specimens collected during laparoscopy<sup>9</sup> – all together, an



invasive procedure that requires specialised materials, trained practitioners, and time. An additional component to the difficulty of diagnosing endometriosis is the lack of awareness of the disease, both by the patient and general practitioners.<sup>2,10</sup> Indeed, it is strongly ingrained in our society to expect painful periods, stigmatisation preventing affected women from seeking help and delaying their diagnosis from 5 to 9 years.<sup>3,11</sup> And a delayed diagnosis means further damage to the affected tissues/organs.

Even if a patient makes it to the diagnosis there is, unfortunately, currently no cure for this disease. There are however palliative treatments to ease the symptoms and limit the spread of the disease. The first line of treatment is to relieve the pain during the period with analgesics such as ibuprofen or paracetamol. To tackle endometriosis lesions and limit their spread, two options are currently available: hormonal treatment and surgery. Given that endometriosis is an estrogen-dominant condition,<sup>8</sup> controlling the secretion and circulation of estrogen could limit the development of the disease. The most widely used hormonal treatment for endometriosis is the contraceptive pill. In addition to limiting the disease, the pill will also limit dysmenorrhea (severe and frequent menstrual cramps and pain during the period) or

Although the painted landscape seems pretty dark, there are specks of hope for the treatment of endometriosis.

chronic pelvic pain. Other hormonal treatments such as gonadotropin-releasing hormone (GnRH) agonists and aromatase inhibitors have a similar mechanism of action,<sup>9</sup> although their effectiveness holds limited evidence.<sup>12</sup> In the case of hormone-resistant endometriosis, surgery can be considered to remove lesions and endometriotic adhesions.<sup>9</sup> Unfortunately, lesions reappear post-surgery and progress in approximately 30% of cases.<sup>13</sup>

Although the painted landscape seems pretty dark, there are specks of hope for the treatment of endometriosis. First, in tackling the challenge of non-invasive, accurate, and sensitive diagnosis of endometriosis, promising biomarker candidates emerged. For instance, patients with endometriosis displayed higher VEGF-A (an angiogenic factor promoting vascularisation) and lower mir-135a (a small single-stranded non-coding RNA molecule) levels compared to patients without endometriosis.<sup>14-16</sup> Both biomarkers could be analysed from a simple blood sample – a cheaper, faster, and less invasive procedure than surgery. Second, there are currently 15 clinical trials testing non-hormonal therapies as alternatives to analgesics and hormonal treatments for endometriosis-related pain.<sup>2</sup> Finally, the microbiota (the population of bacteria and other

microorganisms we host in our body) of the gut and of the female genital tract are emerging topics in both the diagnosis and treatment of endometriosis. Indeed, it was observed that the genital microbiome (the genetic characterisation of the microbiota) of women with endometriosis is different compared to controls and could be associated with the severity of the disease.<sup>17</sup> Besides, women with endometriosis displayed a reduced microbiome diversity and an increased proportion of potentially pathogenic microbes in both gut and genital systems compared to healthy women.<sup>18</sup> Harvesting the power of the microbiota, two clinical trials showed a decrease in endometriosis-related pain after oral administration of a pool of *Lactobacillus* strains.<sup>19,20</sup> These encouraging studies call for further analysis of the relationship between microbiome and endometriosis, which altogether would allow diagnosis options and potential treatments and/or prevention using pre- and/or probiotics.

Despite being a common condition, endometriosis remains nowadays a challenge for millions of women worldwide, with a diagnosis like an obstacle course and limited treatment options. There is however at least one thing that everyone can do to fight the disease even if you are not directly affected – raising awareness. Fighting the stigmatisation of painful periods will help ensure an early diagnosis, improve the management of the disease, and promote research and clinical trials, which is key to providing new therapeutic options.

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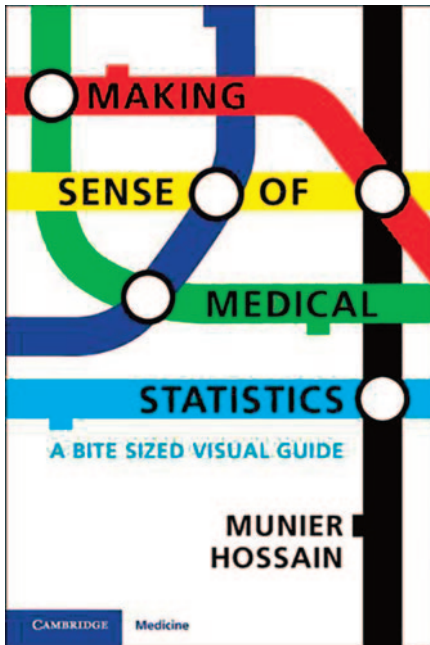


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# In the Bookstores



## Making Sense of Medical Statistics

**A Bite Sized Visual Guide**

By Munier Hossain

Cambridge University Press, 2021

ISBN 9781108978156, paperback, 188 pages;

£15.24

**W**ith more and more of us reading books online or on Kindles, it is hard to judge the size of a book. Therefore, I requested a print version of this book so that I could judge if “a bite sized visual guide” really was what we would call “bite sized”, or if in fact, I would receive a tome that was more akin to *War and Peace*. When the relatively dinky 188 pages plopped onto my doormat I was more than relieved!

Munier Hossain is a consultant orthopaedic surgeon who teaches statistics and evidence-based healthcare to medical students, as well as being an editor of the *Bone and Joint Journal*. As such, he is well placed to identify which statistical tests are of most interest in clinical research and practice. As he notes, clinicians (and

medical writers!) do not need to learn the statistical formulae – but we do need to understand the concepts behind them, which tests are most appropriate, and how to interpret the results. This book aims to explain all of this in very easy to digest chunks.

Dr Hossain states that his aim is to make the book “fun, relevant, interactive and visual” and to a large extent, I think that he has achieved this well. It is a very easy-to-read book, split into 19 chapters that each deal with a different topic, but with increasing complexity as you might expect. The pages have sidebars with icons representing interesting anecdotes, key information, and questions to think about, and each chapter starts with learning objectives and ends with the take home messages. This “topping and tailing” is especially helpful if you just want to dip in for a quick refresher on a particular test or topic. For those wanting more information, more in-depth discussions, or practice questions beyond the questions-and-answers sections given in the book, there is more information available online.

Having discrete, manageable sections was really useful for me – it was easy to pick up and put down the book, and to skip to chapters that I was particularly interested in. The anecdotes were not especially aimed at physicians, and so were interesting for everyone, and the bullet points were especially helpful. I found the “Did you know” questions a bit distracting and at times annoying, but I think that was a personal preference and I’m sure that there are others who prefer to learn by being challenged with questions in that way (I quickly adjusted to ignoring the logo when I saw

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it on the sidebar). However, the take home messages and Q&A sections at the end of each chapter were excellent and helped to consolidate the learning from the chapter well.

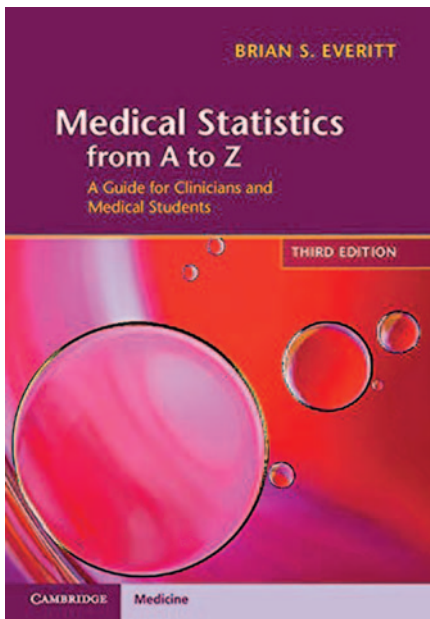
Although this is a small book, the graphics were well done and very legible. The final chapter discussed aspects of the coronavirus epidemic, which is both very timely and fascinating to read from a statistical viewpoint. The author cleverly uses the mishandling of the coronavirus statistics in government briefings to explain how data can be manipulated during clinical trial planning and reporting – one of the best ways to explain this that I have seen!

I think this is one of the best medical statistical texts that I have read and would be

**I think this is one of the best medical statistical texts that I have read and would be particularly good for medical writers either brand new to the subject and needing to get started on statistics, or for those just needing a quick refresher.**

particularly good for medical writers either brand new to the subject and needing to get started on statistics, or for those just needing a quick refresher. It is less useful for writers wanting a comprehensive coverage of medical statistical tests, their origins, and derivations – but perhaps more of that could be found online in the book’s “more information” (I confess that I did not look into this in any detail!). The Glossary section at the end is well worth a look and is almost worth having the book for that alone. Overall, I would highly recommend this book for

medical writers – there are few of us who don’t need to check up on some stats tests every once in a while, and this is a quick, easy, and highly digestible way to do it!



## Medical Statistics from A to Z

### A Guide for Clinicians and Medical Students

By Brian S Everitt

Cambridge University Press, 2021  
ISBN 978-1108826464 (paperback),  
3rd Edition, 292 pages; £29.99

**B**rian Everitt is Professor Emeritus at King's College, London, and has written many books on complex statistical methods. However, unlike many of his other books, *Medical Statistics from A to Z* is aimed at those with little experience of medical research and clinical trials. The compact guide undertakes to explain “non-technical definitions” of complex statistical and clinical terminology. The terms defined in the book cover a wide range of words, phrases, and abbreviations associated with medical statistics, epidemiological, and clinical research. In this third edition 150 new definitions have been added to *Medical Statistics from A to Z* to provide over 1500 terms in total.

As expected from the title, the terms are ordered alphabetically, and a suitable definition provided for each term or phrase. Additionally, within most definitions the author has provided references to allow a reader to access further information if they wish to delve deeper into the subject. This turns *Medical Statistics from A to Z* into a more superior reference handbook.

To assist the reader further, Professor Everitt has provided internal cross-references (noted in a different typeface) to guide the reader to related and useful clarifications elsewhere in the book. From my hard copy version, I cannot determine if these internal cross-references are all active links. From Amazon, I can see that some links in the Kindle version are active; if this function is fully active it will be very useful and allow the reader to efficiently navigate the connected points of information in the book.

The author has included 88 example figures to align with relevant associated definitions. For example, to supplement the definition of “scatter diagram” there are sample scatter plots provided. Within the definition the author usefully explains how to interpret each of the example plots presented in the accompanying figure. Additionally, cross references to other related data display methods are provided (namely: bubble plot, correlation coefficient, and scatterplot matrix) all of which have their own example figures to help the reader follow the explanation. The presentation of relevant figures embedded alongside descriptive explanations is useful in helping the non-statistician understand terms more fully.

As well as providing definitions, many statistical and clinical abbreviations are also defined. For instance, NOEL (no observed effect level) and NNT (number needed to treat). For pharmacokinetic terms AUC (area under the curve),  $T_{\max}$  (author definition: the time at which a patient's highest recorded value occurs),  $C_{\max}$  (author definition: the highest recorded response value for a subject) a figure depicting a

Reviewed by Alison McIntosh

time course of plasma concentration is provided to illustrate these pharmacokinetic terms. Again, use of an illustrative figure amplifies the helpfulness of the descriptive explanation.

Alongside some definitions, the author offers his own sage advice for inexperienced writers, for example: “Graphical deception” he defines as “...displays which may mislead the unwary either by design or error...” A misleading presentation of data should not be employed by writers under any circumstances, and by highlighting and defining this term the author is providing a reminder to be on the lookout for data which might be presented by others in this misleading way.

For those who are not experts in statistics, there are useful pointers and warnings using text presented in shaded boxes to highlight some difficulties that can occur with certain statistical techniques. For example:

“Imputation: Single imputation of missing values ‘invents’ data, which may lead to overstatements of precision, that is, standard errors that are underestimated, p-values of tests that are too small and confidence intervals that do not cover the true parameter at the stated rate. Multiple imputation overcomes some of these problems.”

Constructing the book as an A-Z of medical statistics allows the reader to quickly and easily identify definitions and clarifications which are often accompanied by the author's own nuggets of statistical wisdom. One minor point: a few non-statistical definitions look out of place, (e.g., “internet” or “Electronic mail”) and are likely to be a left over from an earlier edition (first published in 2003). They do not detract from the usefulness of the book and overall, this book should be a welcome resource for medical writers who are not statistical experts.



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 standardised 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

# Good Writing Practice

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## Syntactic Grammar Distraction

### Omission: Indefinite Article



#### Introduction

**T**he indefinite article *a* functions as a determiner before a singular count noun, either tangible (*a human*) or abstract (*a trait*). This determiner indicates that the noun is either being mentioned for the first time or is general (indefinite) in meaning, or both. Its omission elicits a temporary gap to an English-as-a-first language reader because indefinite article usage, inherent to the language, is intuitively recognised. However, to an English-as-a-second-language reader, especially whose native language lacks articles, the omission of *a* is not intuitively recognised.

Two tests for identifying a singular count noun are it is (1) pluralisable (e.g., *humans*) or (2) precedable by another type of determiner: indefinite pronoun (*many humans*) or a numeral (*10 humans*). Another test is to read the sentence aloud. Often a reader will spontaneously add the article because the ear is more sensitive than the eye.

In contrast, a non-count noun (mass noun) cannot be pluralised (*informations*) nor preceded by another determiner: indefinite pronoun (*many information*) or a numeral (*10 information*).

The indefinite article is not as nuanced as is

the definite article, which can convey emphasis. One exception is whether the noun is to be marked by *an* because the first syllable of the noun is pronounced as a vowel.

#### Experimental sections

##### Part 1 – Results section: result statement/observation

###### **Example: Article omission**

*Phagocytosis by dermal fibroblast increased.*

###### **Revision 1**

*Phagocytosis by **a** dermal fibroblast increased.*

###### **Revision 2**

*Phagocytosis by dermal fibroblasts increased.*

###### **Revision 3**

*Phagocytosis by **the** dermal fibroblasts increased.*

#### Notes

Plurality is preferred (Revision 2) because the focus on a single fibroblast is unlikely. Furthermore, in the Results section, it is likely that the focus is on a specific group of already mentioned fibroblasts, justifying the usage of the inter-sentence continuity marker *the* (Revision 3).

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##### Part 2– Materials and Methods section: method

###### **Example: Article omission**

*UWB Waveform was constructed by summing a complete, orthonormal, time-dependent basis set by using an optimal set of integers as the coefficients.*

###### **Revision**

*A UWB Waveform was constructed by summing a complete, orthonormal, time-dependent basis set by using an optimal set of integers as the coefficients.*

#### Notes

Once recognised as a count noun, another consideration is whether the noun is pre-modified (post-modification does not affect indefinite article determiner usage). The presence of the



pre-modifier *UWB* should not obscure the singular countable nature of *Waveform*. The article *a* is required before *UWB* because *U* is pronounced as the consonant *yoo* (see Table). The same applies to *unique*. Another vowel-written but consonant-sounding word is *one* (pronounced as *won*) as in *a one-page report*.

## Contextual Sections

### Part 1 – Introduction section: research problem background

#### Example: Article omission

*In human, the craniosynostosis trait is present in all individuals who carry the Pro7His mutation.*

#### Revision 1

*In a human, the craniosynostosis trait is present in all individuals who carry the Pro7His mutation.*

#### Revision 2

*In humans, the craniosynostosis trait is present in all individuals who carry the Pro7His mutation.*

## Notes

The revision options are: *In human* could be revised by addition of the *a* or conversion into the plural *humans*. In the context of the sentence constituent all individuals, the plural *humans* (Revision 2) seems to be appropriate.

## Summary

Indefinite article usage decision guidelines may be summarised as follows:

Syntactic situation	Example	Guideline	Revision
A count noun	<i>Phagocytosis by dermal fibroblast</i>	Indefinite article addition	<i>Phagocytosis by a dermal fibroblast</i>
		Science: individual cell not being studied	<i>Phagocytosis by dermal fibroblasts</i>
		Section of journal article: in the Results section a specific group of fibroblasts were probably pre-mentioned in the Materials and Method section	<i>Phagocytosis by the dermal fibroblasts</i>
A count noun preceded by a noun premodifier	<i>UWB waveform was constructed</i>	<i>In human</i>	<i>In a human</i>
		<i>In a human</i>	<i>In humans</i>
A count noun preceded by a noun premodifier	<i>UWB waveform was constructed</i>	The first syllable of the premodifier is pronounced as the consonant <i>yoo</i> not a vowel	<i>A UWB waveform was constructed</i>

## Determinants of indefinite article A or An usage

Determinant	Pronunciation of first syllable	Choice of determiner
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### Vowel-written and vowel pronounced syllable

<i>ATM network</i> <sup>1</sup>	A	<b>An</b> <i>ATM network</i>
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### Consonant-written and consonant pronounced syllable

<i>Historic importance</i>	His	<b>A</b> <i>historic event</i>
----------------------------	-----	--------------------------------

### Vowel-written but consonant pronounced syllable

<i>One-page report</i>	Won	<b>A</b> <i>one-page report</i>
<i>Unique approach</i>	Yoo	<b>A</b> <i>unique approach</i>

### Consonant-written but vowel pronounced syllable

<i>MTE membrane</i>	Em	<b>An</b> <i>MTE membrane</i>
<i>NEN-inhibited enzyme</i>	En	<b>An</b> <i>NEN-inhibited enzyme</i>
<i>Hour-long incubation</i>	Ohr	<b>An</b> <i>hour-long incubation</i>
<i>RCP</i>	Ar	<b>An</b> <i>RCP</i>
<i>SDS</i>	Es	<b>An</b> <i>SDS</i>

- 1 For vowel-pronounced abbreviations, *an* is also common: *an ATM network*. A.T.M. is pronounced letter-by-letter (an initialism) rather than by syllables as is the acronym (e.g., RADAR).

# Erratum: Ins and outs of environmental risk assessments (ERAs) of medicinal products for human use

**A**n article that appeared in the March 2022 issue of *Medical Writing* mistakenly cited the wrong version of environmental risk assessment guidelines in two places and included incomplete information in the Acknowledgments section. The errors have been corrected in the PDF posted online for the article “Ins and outs of environmental risk assessments (ERAs) of medicinal products for human use”.

On p. 26, the heading in the third column incorrectly mentioned EMEA/CHMP/SWP/4447/00 Rev. 1 (2018). It should have said: EMEA/CHMP/SWP/4447/00/Corr2 (2006).

On p. 28, in the first column, Reference 7 was cited after the following sentence: “This is so that those in water management are able to monitor substances of concern.” It instead should have cited the following document:

EMA/CHMP/SWP/4447/00 Rev.1. Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. 2018 [cited 2021 Nov 12]. Available from: [https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf)

This document is now listed as Reference 15 in the online PDF.

On p. 29, the acknowledgments should have thanked Diana Radovan for peer review.

## Reference

Nagarajan A, Uegaki K. Ins and outs of environmental risk assessments (ERAs) of medicinal products for human use. *Med Writ*. 2022;31(1):26-9.

# The Crofter: Sustainable Communications

SECTION EDITOR



Kimi Uegaki  
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## Editorial

Greeting from the croft! During my non-linear career path, there has been one recurring theme that always rang true: “Context matters”. As a physical therapist working in a rehabilitation centre, understanding my clients’ social roles, home environment, and family situation was critical for determining relevant therapy goals and activities. As a researcher studying work disability prevention, it was clear that contextual factors such as the socio-political system of the

country where the injured worker lived, and workplace culture and dynamics influenced return-to-work. And now as a medical writer, making sure I understand the (strategic) context of a given document and the target audience is an essential step of my writing process.

This past spring, I had the opportunity to speak virtually with Gomotsegang Fred Molelekwa, PhD, who is a public and environmental health expert and chemical engineer living in South Africa. In early 2020, he was heavily involved in efforts to

increase general awareness about public health intervention measures regarding COVID-19 in South Africa. It was eye-opening to learn about his context and the challenges he faced and continues to face with health communication, also for non-pandemic related issues. In this issue of The Crofter, Fred shares his story and strategies for improvement. I hope you find it as interesting to read as I did, when hearing it first-hand.

Best,  
Kimi

## Challenges and strategies for effective health communication in middle- and low-income countries: COVID-19 lessons from South Africa

### An interview with Gomotsegang Fred Molelekwa (PhD),

Associate: Research and Innovation at Tshwane University of Technology, South Africa

**Crofter:** As medical writers and communicators, one of the first things we need to understand before we start writing is our audience and their context. Can you describe the South African audience and their context?

**GFM:** Yes, I will start by giving you the historical context of South Africa. South Africa is one of the most unequal societies in the world and this could be attributed to the Apartheid Regime. The segregation and inequalities in education, employment, and infrastructure that arose during Apartheid still act as barriers to our efforts to communicate effectively with all citizens across the country. They are barriers to equal access to information in general, and health information in particular.

Apartheid influenced settlement patterns, for example, rural vs. urban areas, and in urban settlements, suburbs vs. townships. There were divisions along lines of race (White, Black, Coloured, and Indian) and ethnicity among Africans. Along ethnic lines, different languages are spoken; this is reflected in the nine provinces

and the 11 official languages that are recognised in South Africa (i.e. nine African languages, English, and Afrikaans).

After Apartheid was abolished in 1994, a democratic government was established. This government developed and implemented a National Reconstruction and Development Plan to address the inequalities of the past Apartheid regime. However, not all aspects thereof have been resolved. And the opportunities for equal access to education, employment, and the quality infrastructure (e.g. telecommunications, electricity, sanitary systems, roads) still differ along settlement patterns. For example, the suburbs (which are predominantly occupied by White South Africans) in metropolitan municipalities such as City of Johannesburg, City of Cape Town, eThekweni, and City of Ekurhuleni have better quality of and access to infrastructure than townships and rural areas, which are predominantly occupied by Africans. With regard to communication, the poor quality of telecommunication and electricity infrastructure in the rural settings means that citizens have

unreliable TV, radio, or telephone connections. It is also important to note that the literacy level is lower in rural areas than urban areas, which means that people in rural areas prefer to communicate in their respective vernacular language to express themselves and better understand each other. This aspect of literacy level is critical when disseminating health information in South Africa.

**Crofter:** The COVID-19 pandemic has demonstrated in more ways than one than one how, despite all our best intentions, communicating with the public effectively can be very challenging. In the Netherlands, for example, the public health messaging was undermined by inconsistent and contradictory statements, among other issues. South Africa is the hardest hit country on the African continent. Can you share some examples of communication efforts that worked as well as some of the problems that you observed?

**GFM:** You are correct that South Africa is the hardest hit country on the African continent. In

terms of COVID-19 messaging, South Africa gave consistent messaging which focused on the measures to prevent and control the spread of the SARS-CoV-2, the virus that causes COVID-19, and to minimise the impact of this pandemic by saving lives and livelihoods.

The core messaging was on the following:

1. Testing and contact tracing
2. Isolating people who tested positive and quarantining close contacts
3. Wearing of masks in public places
4. Maintaining social distance (1.5 metres)
5. Washing hands with soap and water and/or sanitising hands with 70% alcohol-based sanitiser
6. Disinfecting hard and frequently touched surfaces

After the introduction and administration of the COVID-19 vaccines, the messaging included the importance and effectiveness of the vaccines, including booster shots. For instance, the messages that were carried out indicated that “Vaccines are safe, effective against severe illnesses, hospitalisation, and death”. These messages were disseminated on radio, television, social media platforms, and websites, etc. However, the messages were mostly in English.

People were also cautioned against “misinformation and fake news” about COVID-19, SARS-CoV-2, and the vaccines, among others. They were also encouraged to seek information from reliable sources such as the WHO, Africa CDC, National Department of Health, and the National Institute for Communicable Diseases (NICD).

There were also regular updates given by the Minister of Health, premiers, and the provincial Members of the Executive Council for Health (i.e. Health MECs) in all the nine provinces, and government officials from various departments, especially the Department of Health, about the status of the pandemic with specific focus on the number of cases (new and cumulative cases), deaths, and recoveries.

Despite these positive aspects, the country also had some challenges in communicating COVID-19-related messages to all South Africans. The problem of electricity load shedding (i.e. scheduled moments when electrical grids get shut down) meant that people missed out on messages broadcast by the radio or television if the broadcast coincided with a grid shut down. Again, considering the low literacy level in rural areas, people who do not understand English did not understand the messages that were disseminated in English through posters, radio or TV advertisements, or



on social media platforms. It should be noted that government made attempts to communicate those messages in vernacular, particularly on radio and television. However, poor, or the lack of, telecommunication infrastructure in most rural areas meant that some people did not get the valuable information, which might have contributed to non-compliant behaviour and vaccine hesitancy displayed by some people across the country.

Another challenge of reaching the public was the combination of high cost of data and high unemployment rate, particularly among young people. The majority of these people could not afford to buy data to view videos or listen to audio campaigns that were being streamed online. Many of them could only afford a limited amount of data, which they mostly used to stay in contact with family and friends rather than use it to listen to educational podcasts or videos, which were mainly in English.

In addition to the challenge of reaching many

people due to inadequate telecommunication infrastructure, there was low participation by health professionals (from public and private sectors) in the dissemination of information in vernacular official languages, particularly on television and radio. Therefore, most of the time, the information that was disseminated by non-health professionals about the general intervention measures, and information about the epidemiology of the disease, particularly the structure and behaviour of the virus, and mode of transmission, was not well articulated. Furthermore, the non-health professionals could not give information about the relationship between the structure and behaviour of SARS-CoV-2 and the recommended intervention measures, for instance, the fact that SARS-CoV-2 is an enveloped virus (i.e. lipid bilayer envelope), the envelope makes this virus susceptible to destruction upon exposure to detergents and organic solvents, and hence, the need to use alcohol-based sanitiser or wash hands

with soap and water for at least 20 seconds. Another fact not communicated was that enveloped viruses such as SARS-CoV-2 may only survive outside host environments for a limited time and they need to be transferred directly from one host to another as soon as possible in order for them to continue to survive, and hence, it is important for those who tested positive for COVID-19 to isolate themselves for 7 days from the date of testing positive in order to allow the virus to wane off and to avoid infecting other people.

Upon realising this gap in March 2020, I contacted one of the radio stations called Motsweding FM and offered to give COVID-19-related talks on a weekly basis. Motsweding FM is owned by a public broadcaster, the South African Broadcasting Corporation (SABC). This radio station has just over 3 million listeners per year (2021 figures),<sup>1</sup> and I gave talks from April 2020 until March 2022 to over 1 million listeners on the programme called, "Di Rage". The talks covered various aspects of the disease:

- *Myths and Facts About COVID-19 and SARS-CoV-2*
- *Asymptomatic Spreaders: Young People with COVID-19*
- *Messaging Strategies to Encourage People to Get the COVID-19 Vaccine*
- *Concerns Over Increased COVID-19 Infection Rate After Local Government Elections*
- *The Role of Stakeholders in Increasing COVID-19 Vaccination in South Africa*
- *When People Choose Not to Vaccinate with COVID-19: Vaccine-Risks and Responsibilities*
- *Pointing the Finger at Unvaccinated People for the Spread of COVID-19 in South Africa*
- *Waste Management During COVID-19 Pandemic*
- *More Young People are Getting Hospitalised as COVID-19 Variants Spread*
- *Measures to Contain COVID-19 After the Lifting of the National State of Disaster in SA*

The aim of my talks was to educate the public about the different epidemiological aspects of SARS-CoV-2 so that they would understand why it was important to adopt certain hygiene habits. I wrote the scripts in English and translated them to Setswana, which is the official vernacular language that is spoken on Motsweding FM and it is also the language that I speak at home. I offered my English scripts to other health professionals, particularly the environmental health practitioners who speak different vernacular official languages and asked them to translate it to their respective languages and give those talks on the radio stations that are speaking

their languages and share the messages with the listeners of those radio stations. However, they did not accept my offer and the listeners of other vernacular languages missed out on this information. It is important to mention that there was another lady, Ms Pontsho Pilane, Head of Communications at the Wits Reproductive Health and HIV Institute (Wits RHI), who also gave COVID-19-related talks on Motsweding FM, and she did that on weekdays from February 2020 until end of March 2022.

**Crofter: Taking stock of the challenges and the successes, can you describe the changes and strategies you hope to implement in South Africa in order to improve health communications?**

**GF:**First and foremost, government should improve the telecommunications infrastructure across the country, especially in rural areas and townships. Digital communication infrastructure should be provided and improved to encourage uptake and use of digital health messages. Trustworthy sources of information must be easily accessible and should counter false or fake news, myths, or misinformation.

There is a need to develop a national health communication strategy. It is therefore imperative that all the relevant stakeholders are involved (e.g. government, traditional councils, industry, universities, colleges, community organisations, community members, etc.) during the development and implementation of that strategy. The strategy should cover health and hygiene promotion, disease outbreaks, non-communicable diseases, explanation of concepts, sustainability, etc. Additionally, the strategy should be mindful of the 11 official languages in the country. This means that the strategy should be written in all 11 official languages and messages should also be shared in all the official languages.

Health professionals, especially epidemiologists and medical scientists should actively participate in health education and awareness raising programmes and should speak in vernacular to ensure that their target audience hear and understand their message. Education and awareness raising campaigns must be standardised, however, the implementation thereof should be adapted to suit the local area.

There is a need for close collaboration between the health professionals in the public and private sectors in terms of developing and implementing the health communication strategy.

Institutions of higher learning, such as

universities and colleges should also take part in community education and awareness raising by creating relevant messages and content for the targeted groups.

Medical writers and other health writers (journalists) and experts should, through individual efforts or their respective associations, establish or improve their footprint across the country and ensure easy access to reliable health information. Moreover, they should create relevant health content to address significant health challenges, including climate change effects on health, food security, waste management, etc. Most importantly, local medical writers and other health writers should collaborate with content experts and other medical/health communicators around the world. These approaches would go a long way in ensuring that citizens are enlightened about health-related matters, thus improving their quality of life and health.

## Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by Tshwane University of Technology or EMWA.

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# Biotechnology

SECTION EDITOR



Jennifer Bell

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## Editorial

Ahmad Nazzal defines biotechnology as, “a field of science that involves using living organisms and organic substances to create or modify environments, produce goods, or improve human health.”

Biotechnology is a vast topic and can be defined by using biological systems and living organisms in production processes. Biotechnology is commonly employed to make medical treatments using biomolecules and living cells.

It is vital that the massive amount of raw data generated during omics medical research is understood for medical treatments to be

successful. Unfortunately, Big Data has resulted in a data bottleneck where lots of data are not processed because omics data processing technology needs to catch up. For some perspective, a 2015 estimate says about 40 petabytes of genomic data are produced at a population scale yearly.<sup>1</sup> One petabyte equals 1000 terabytes, and one terabyte equals one million megabytes. Almost 900 megabytes of data are needed to store information from one human genome.

Ahmad explains that bioinformatics is where biology, computer science, and information technology meet to help process large data sets. He glances over artificial intelligence (AI)

regulation as a medical device because how to regulate it remains unclear. He writes about genomics and proteomics and how artificial intelligence is developing to process Big Data. Ahmad highlights the importance of public perceptions concerning how AI and biotechnology are embraced in the world.

I want to thank Ahmad for helping me to understand the developing role of AI in bioinformatics and biotechnology.

Jennifer Bell

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## Artificial intelligence, biotechnology, and trust

**A**rtificial intelligence (AI) is changing biotechnology. In this article, I discuss recent breakthroughs of AI in biotechnology, obstacles preventing faster progress, the future of the field, and the major role medical writers can play in building trust in the public about the future of AI in biotechnology.

First, let's look at the history of AI. In the 1950s, scientists seriously started to debate inventing machines that mimic human intelligence, and when breakthroughs in our understanding of DNA occurred. The field of artificial intelligence (AI) was born.<sup>1</sup> Today, AI can perform tasks such as visual perception, speech recognition, decision-making, translation between languages, and analysing data.<sup>2</sup>

However, AI is the new kid on the block when it comes to biotechnology.<sup>3</sup> Biotechnology is a field of science that involves using living organisms and organic substances to create or modify environments, produce goods, or improve human health.<sup>4</sup> AI is making it easier and faster to find new drug targets for diseases, detect diseases and harmful mutations, programme synthetic DNA, and analyse DNA sequence data.<sup>3</sup>

### AI regulations in healthcare

The volume of data that AI can process is increasing. This makes it difficult to assess the quality and safety of AI-driven healthcare solutions. Therefore, in 2019, the US published a



discussion paper that explains the approach to premarket review for AI-driven healthcare software when used in conjunction with a medical device.<sup>5</sup> Then, in 2021, the International Coalition of Medicines Regulatory Authorities published a report that provided recommendations for regulating therapies using AI. The report recommended adopting a risk-based approach, establishing governance structures, and fostering data reliability. Furthermore, it supported transparency, understanding, and real-world monitoring of patient functioning.<sup>6</sup> However, it is unclear how to keep up with the pace of innovation while regulating algorithms as medical devices.<sup>7</sup>

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### Breakthroughs

Bioinformatics, also known as computational biology, merges biology, computer science, and information technology. Bioinformatics accelerated areas of biotechnology that includes gene and protein sequencing, identification, prediction of function, understanding of complexity, structure and folding, and drug design and development.<sup>8</sup> AI has helped to make significant advances in biotechnology and bioinformatics.

### Advances in genomics

Genomics is the study of the sequence and function of genes. The human genome is a set of approximately 3 billion base pairs on 23 pairs of chromosomes,<sup>9</sup> with differences between individuals called genetic variations.<sup>10</sup> There is a vast amount of data for each human being that standard statistical tools cannot analyse.<sup>11</sup> However, AI-based applications promise to help in this area. For example, DeepVariant,<sup>12</sup> a convolutional neural network, outperformed standard tools on variant-calling tasks.<sup>13</sup>

Furthermore, AI algorithms can improve variant classification and predict the impact of those variations. For example, PrimateAI,<sup>14</sup>



a convolutional neural network, outperformed previous methods in variation detection. It was trained on data from 120,000 human samples and showed superior performance compared to other variant pathogenicity prediction tools.<sup>15</sup>

However, not all genes code for proteins. Understanding non-coding genes remains an open challenge for the field.<sup>16</sup> It is estimated that up to 11% of rare genetic disorder causes could be traced to non-coding genes.<sup>17</sup> AI is expected to improve our understanding of non-coding genetic variations. For example, a deep layer neural network called SpliceAI<sup>18</sup> was able to predict non-coding genetic variants.<sup>17</sup>

The Human Genome Project highlights many genomics field advances. On October 1, 1990, the Human Genome Project was officially launched after planning in the late 1980s. It took scientists 13 years of work and almost US \$3 billion in funds to map the human genome, a mosaic of sequences from 13 individuals.<sup>9,19</sup> However, even today, amendments are being made to the human genome reference sequence. Advances in the genome sequencing field have led to considerable reductions in the cost of genome sequencing. In 2014, the US\$ 1000 genome was announced, and 20,000 human genomes could be sequenced in

1 year.<sup>20,21</sup> Costs have continued to reduce, and a human genome can be sequenced for US\$ 600 with the US\$ 100 genome not far behind due to advances in AI and computing.<sup>22</sup>

#### The protein folding problem and AI

Proteins are the building units and the working molecules of the cells. They are made up of chains of amino acids, which can be arranged in a variety of ways in 3D space. Therefore, studying protein folding is difficult. In fact, it is referred to as a “grand challenge” in biology.

In biology, it is crucial to understand the way a protein folds because it reveals its function.<sup>23</sup>

Scientists study protein folding using x-ray crystallography – an expensive, time-consuming, and error-prone process.<sup>24</sup> In theory, it is possible to determine protein structure by reading its amino acid sequence – this was impossible until 2020.

In December 2020, Google DeepMind<sup>25</sup> – a division of Alphabet Inc.<sup>26</sup> responsible for developing AI – introduced a neural network-based model, AlphaFold,<sup>27</sup> to accurately predict how proteins fold. This was acclaimed as the solution to the 50-year-old protein folding problem.<sup>28,29</sup> Three months later, and in partnership with the European Molecular

Biology Laboratory-European Bioinformatics Institute (EMBL-EBI), DeepMind launched the AlphaFold Protein Structure Database. Now, scientists can access and download the shape of every single protein in the human body and proteins of 20 additional organisms. This is expected to help scientists find solutions to antibiotic resistance, microplastic pollution, and climate change – a One Health approach.<sup>30</sup>

#### Drug discovery and AI

Drug discovery is an expensive, complex, and uncertain process.<sup>31</sup> The process of drug development can take around 12 years and costs up to €3 billion.<sup>32</sup> Drug development can be divided into three stages: hypothesis generation, candidate development, and commercialisation. Hypothesis generation involves target identification and validation, assay development, and lead generation. Once a couple of candidate leads are generated, the drug goes into animal studies for optimisation. Optimisation is an elaborate, time-intensive, and costly process. Once optimisation is done, first-in-human testing starts with a Phase IA clinical trial, in which the drug is tested on a small number of healthy volunteers. This is followed by Phase IB trials to establish safety, steady-state pharmacokinetics, and maximum tolerated dose. If the drug provides a

Without data,  
there can be no  
usage of AI.

proof of concept, it can move forward to larger randomised Phase II and Phase III trials to establish safety and efficacy. This is followed by marketing and continuous global optimisation.<sup>33</sup>

AI will enhance the process substantially.<sup>34</sup> Machine learning or deep learning – both sub-topics in the field of AI – can be used to discover and optimise therapeutic candidates faster.<sup>35</sup> In addition, AI is expected to cut down the costs of drug discovery. According to a one market size analysis, AI has the potential to save US\$ 70 billion by the year 2028 in the drug discovery field.<sup>36</sup> Therefore, leading pharma companies are forging partnerships with AI start-ups and companies.<sup>34</sup> As such, faster drug discovery will require more medical writers to help get approvals from regulatory agencies.

## Challenges

New technologies from AI have made significant advances in data-driven fields like biotechnology and medicine.<sup>37</sup> This AI-driven innovation in biotechnology and medicine will continue to increase.<sup>38</sup> However, this progress faces challenges.<sup>39</sup>

### The data set challenge

One of the biggest challenges in applying AI to biotechnology, medicine, and healthcare is the lack of properly annotated, standardised, and non-biased data sets. Without data, there can be no usage of AI.<sup>40</sup>

AI specialists train AI algorithms on real-world data.<sup>41</sup> In AI there are two approaches to train an algorithm: supervised learning and unsupervised learning. In supervised learning we need to input a set of input data and to have the desired output labelled by human experts. The input data is made up of a set of things or events which can be repeated in a predictable pattern. The desired output is a prediction of the next event in the sequence. For example, in the prediction of an alphabet, the desired output is a letter. The input is a sequence of letters. It is a lot like teaching a small child the alphabet. In teaching a small child the alphabet, a person can tell the child what the alphabet is and what sound each letter makes. This would be the input data, and the desired output would be the child recognising the letter once presented. Thus, learning the alphabet.

As such, biased data sets will create biased AI. Many AI algorithms are trained with data sets that consist of data that reflect the biases of the culture that created it. In 2019, researchers found that an algorithm – used in US hospitals to predict which patients need extra medical care – favoured white patients over black patients. This

algorithm affected 200 million patients.<sup>42</sup> To create an ethical non-biased benevolent AI, we need to assess data sets for biases, inequities, and discriminations.<sup>43</sup> Nevertheless, credible data sets remain a challenge for AI progress in data-driven fields including biotechnology.

### The mindset challenge and building trust

AI is a powerful tool that could help but also could magnify flaws in the system at a damaging scale. Troncoso suggested that the greatest challenge to the usage of AI in healthcare is to change mindsets towards AI.<sup>44</sup>

Troncoso proposed that this challenge is representative of each society's mindset. And to achieve a change in attitudes, we need to educate and increase awareness of AI, to make AI more explainable, and to build trust between parties involved in the process. By the same token, it is recommended to implement ethical frameworks, encouraging positive behavioural intentions behind using AI and strike a balance between the exchange of individual data and the public for the greater good.<sup>44</sup>

### The role of medical writers in building trust

AI is becoming more present in the world of biotechnology, where it will work with human scientists to solve real-world problems. Unfortunately, biotechnology often suffers from a bad reputation. And negative stories in the media, such as those related to controversies involving biotech companies, do not help.<sup>45</sup> On the other hand, AI has potentially dangerous implications; many scientists believe it could lead to a dystopian future.<sup>46</sup> Both are likely to be difficult for the public to accept without effective communication efforts.

The advancements of biotechnology research are dependent on the use of AI. However, due to the complexity of this field, it requires a significant amount of trust from the public.<sup>47</sup> In order to possess a certain level of trust, the public needs to be able to understand the benefits and risks of biotechnology advancements. Here is where medical communicators come in. Medical writers are experts in writing complex medical information and conveying it to others in easy-to-understand language.

The main challenge with AI is that it is increasingly difficult to understand – the future of technology is a mystery even to the best

scientists. Despite this, medical writing will be a considerable part of the future. Therefore, medical writers would do well to learn about how AI works. They can easily do so by taking free online courses on the topic and grasping the subject.

## Future

In today's world, we produce a massive amount of biomedical data. AI can digest massive datasets. Thus, in the future, AI will increase the accuracy of diagnosis, reduce the human error rate, and help healthcare professionals deal with a growing workload.<sup>48</sup>

One particularly exciting area is personalised medicine. Future personalised medicine will consider patient's genome to design tailored therapies. AI will make genetic testing more accurate, cheaper, and accessible.<sup>11</sup> Researchers are already using the technology to identify genes that are responsible for rare diseases in individual patients,<sup>49</sup> to understand cancer genomics,<sup>50</sup> and to create new therapies.<sup>34</sup>

## Conclusion

The future of AI is ours to create.

It offers tremendous potential to the fields of medicine and biotechnology. It can help us to accelerate screening and diagnosing diseases, as well as provide better patient-centred healthcare. Nevertheless, we need to be aware of AI's risks, such as aggravating existing social biases. Today, there is more hype and less reality around AI in the biotech industry and start-ups – executives believe there is a gap between what AI can do and what people think it can do.<sup>51</sup> I think that with continuous education we can recognise the hype from reality in the field of AI, determine its risks, and overcome obstacles facing it.

## Disclaimers

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## Disclosures and conflicts of interest

The author declares no conflicts of interest.

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# Pharmacovigilance

## SECTION EDITOR



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### Editorial

The Regulatory Expert Seminar session at the 2021 Spring EMWA Conference took us on an amazing journey through marketing authorisation applications from a regulator's and medical writer's perspective. One of the presentations focussed on the challenges of accelerated reviews, assessments, and timelines from a regulatory affair's perspective, in the context of marketing authorisation submissions for COVID-19 vaccines.

Accelerated regulatory submissions have great impact also on medical writers' tasks and processes. In this article, Arthur Jarov guides us through the challenges of these submissions and shares with us valuable tips to prepare successful documents despite accelerated timelines.

Happy reading!

Tiziana von Bruchhausen  
Chair of the PV SIG

## Accelerated regulatory submissions: Less haste, more speed!

### Introduction

**A**ccelerated regulatory submissions pose major challenges even to the most experienced medical writers. This article discusses those challenges and proposes practical ways of maintaining high document quality and consistency while meeting ambitious submission timelines.

### Why the rush?

Writing a regulatory submission dossier is a major undertaking; it requires thousands of hours of work and usually takes several months. Typically, project teams need 4 months to deliver clinical documents such as the pivotal study Clinical Study Report (CSR) and high-level documents (HLDs), including the Common Technical Document (CTD) Module 2.7 summaries and Module 2.5, the Clinical Overview (CO). A Risk Management Plan (RMP) is also required when applying for a marketing authorisation in some regions and countries.

Although 4 months may seem a reasonable time to prepare those documents, most authoring teams find the experience stressful. The sheer volume of work – combined with challenges in data interpretation and document complexity – can be overwhelming for an inexperienced team. In the dossier, the applicant must not only present all available data on the

investigational product, but also provide a critical analysis of study designs, methodology, and results. Any proposed labelling claim must be justified and backed up by scientific and clinical evidence.

Analysis of clinical safety data presents particular challenges, especially for a new drug application. Safety data are described in detail in CSRs and summarised in the CTD Section 2.7.4, Summary of Clinical Safety (SCS), and the relevant sections of the CO and RMP. An

**At a time when tens of thousands of people were hospitalised with COVID-19 and entire countries went into lockdowns, every day counted.**

important purpose of the evaluation of safety data is the evaluation of Adverse Drug Reactions (ADRs). Depending on the clinical development programme and the indication, safety data from several studies can be pooled to allow detection of less common ADRs. Although some applicants use programmatic methods for ADR detection, this process cannot be fully automated, as it requires careful review by safety physicians and risk management experts. Mistakes in ADR identification can have disastrous consequences for patients, healthcare professionals, and health authorities (HAs), not to mention the legal and financial consequences for the applicant. Therefore, this crucial process cannot be rushed.

Nevertheless, project teams often find themselves under pressure to accelerate submissions. Such pressure can come from company management, HAs, or both. In the United States,

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the Food and Drug Administration (FDA) has launched several initiatives and procedures to shorten the time from submission to drug commercialisation. For example, the Pandemic and All-Hazards Preparedness Reauthorisation Act of 2013 defined the framework for the use of a drug prior to licensing under specific conditions, and the FDA instituted the Emergency Use Authorization (EUA) procedure. The EUA procedure was used extensively in late 2020 and 2021 to authorise the use of COVID-19 vaccines and treatments even before their formal approval by the FDA. The European Medicines Agency and other HAs also started initiatives for acceleration of evaluation procedures in 2020 in response to the pandemic.

At a time when tens of thousands of people were hospitalised with COVID-19 and entire countries went into lockdowns, every day counted. The stakes could not be higher, and neither could the challenges.

### Less haste, more speed!

Accelerated submissions may force teams to reduce document production timelines quite drastically, from 4 months to 4 weeks in cases of hyper-acceleration. Working longer hours is not sufficient to meet such aggressive timelines; after



all, pandemic or not, we still have only 24 hours in a day. Stress, fatigue, and sleep deprivation can lead to errors and result in poor document quality.

Increasing resource allocation to the submission is not sufficient either. Experience shows that resource requirements increase exponentially as timelines shorten. For a 4-week submission, the applicant may need 20 writers, or even more, depending on the complexity of the dossier. In a typical submission, the team writes the pivotal study CSR before the HLDs, as such a staggered process facilitates content reuse. In an accelerated submission, a staggered approach is not always possible, and several documents may be authored in parallel. Maintaining consistency between documents becomes a major challenge for the team. Coordination between writers working on different documents is an issue, and frequent team meetings reduce further the time available for authoring. Teams may find themselves in a situation where they can devote quality time to

their documents only over weekends.

To complicate matters, some events can force the applicant to conduct unforeseen post-hoc analyses or even change the regulatory strategy. Such events include unexpected clinical findings or feedback from HAs. In some cases, major comments from senior stakeholders can trigger a rewrite of some sections or entire documents.

Nevertheless, delivering a high-quality dossier is possible even under hyper-accelerated timelines. Preparation and process optimisation are essential for success, and medical writers should drive this.

#### **Preparation and data-independent authoring**

Teams should start preparing for a submission well in advance, several months before the database lock for pivotal studies. The first step is to set up a kick-off meeting where all submission-

related activities are discussed. The team must devise a clear plan for all these activities, including timelines for data-independent and data-dependent writing of clinical documents. Data-independent writing can start shortly after the meeting.

Teams should also consider preparing a storyboard, a concise, high-level distillation of all aspects of the clinical submission story. The storyboard is used to secure cross-functional alignment on key messages in the dossier and ensure stakeholder's endorsement of the submission strategy. The advantages of a well-developed storyboard are numerous, including an early focus on the desired label, clarity on the submission scope and purpose, and identification of any major scientific issues, gaps, and potential regulatory hurdles. Of course, the storyboard will have to be revised once the pivotal study data become available.

**Preparation and process optimisation are essential for success, and medical writers should drive this**

During the preparation phase, teams may want to go a step further and populate data-dependent sections of clinical documents using shell or dummy tables. This approach helps to ensure that programmed tables and figures are adequate to support the key messages. In addition, it facilitates identification of gaps in statistical analyses.

When preparing for an accelerated submission, some teams want to write complete documents even before the data become available. Writing clinical documents based on dummy data can prove a risky venture, as it may give teams a false sense of security. When it comes to updating the documents using real data, simply replacing the dummy numbers with real ones often proves insufficient, especially in HLDs, which must present a critical analysis of the findings in addition to the factual summarisation of the data. Placeholder text must be rewritten with this imperative in mind.

#### Data interpretation

In the interest of time, some teams want to shorten data interpretation meetings or even skip them altogether and rely on medical writers to interpret the data. I do not recommend this approach as it is counterproductive. Even in the fastest submission, the team must find time to analyse the data and reach cross-functional alignment on the key messages. Early stakeholder buy-in is also important to reduce the risk of major comments during document review.

#### Data-dependent authoring, review, and QC

During the data-dependent authoring phase, medical writers should adhere to lean authoring principles and avoid repetition in HLDs. Instead of repeating information available elsewhere in the dossier, documents should provide links to the relevant CTD sections. Remember that any document available in the electronic CTD is just one click away. Ensure that the level of detail in each section is appropriate. CSRs tend to be more detailed, while HLDs should focus on the findings relevant to the benefit-risk assessment of the product and label claims.

Document review and quality control (QC) can be as challenging as authoring in a fast-paced submission. Reviewer discipline is always important, and it becomes critical when timelines are squeezed. Both the

number of reviews and their duration are reduced. I usually recommend 2 rounds of review for each document. A single review round may be sufficient if the number of reviewers is relatively small, between 10 and 20. In large companies, this number can go much higher, and the authoring team may receive hundreds of comments on a single document. In such cases, consider conducting a team review first, then a stakeholder/management review.

Reviewers should be encouraged to conduct strategic, substantive review. Medical writers have an important role in educating them in good review practice. Comments should be specific, directive, and based on facts rather than personal preferences.

Accelerated submissions do not always allow sufficient time for a separate QC step, therefore QC can be done in parallel with the last round of review. A final QC should be done once all comments are addressed, focusing only on changes made since the last draft. Medical writers should keep redline copies of documents so QC specialists can find those changes easily. Teams should avoid making any amendments to documents after the final QC, as last-minute changes can result in discrepancies and lead to other quality issues.

#### Teamwork, teamwork, teamwork!

Effective teamwork is essential in accelerated submissions. The whole submission team must work as a well-oiled machine, with efficient processes, well-defined roles and responsibilities, and clear communication lines. Any duplication of work should be avoided; content should be reused as much as possible, and teams should refrain from rewriting text that has been reviewed and approved.

#### Submission lead and team structure

Every team of medical writers needs a submission lead. In an accelerated submission, the lead does not always have time to author documents. The rule of thumb is that the team needs at least one person in charge of coordination for every 10 writers. For example, a team of 22 writers requires at least 2 full-time coordinators. Such a large team should consider preparing a charter to ensure everyone is aware of their roles and responsibilities. Also, it may be helpful to set up sub-teams to facilitate coordination and communication, with sub-team leads reporting to the submission lead.

Regular meetings are a necessity; however, teams should find the right balance between attending meetings and working on documents. Submission leads and coordinators should attend all meetings relevant to the submission, while writers of individual documents should attend only the most important ones, for example data interpretation meetings.

#### Time zone differences

International teams can leverage difference in time zones. Such teams can work round the clock while maintaining a reasonable work-life balance for each of their members. This approach can prove particularly effective for global submissions with a large number of documents and challenging timelines. It works best when there is a coordinator in each time zone, for example one in Asia, one in Europe, and one in North America.

#### Ensuring consistency throughout the dossier

As already mentioned, maintaining consistency throughout the dossier is a major challenge in accelerated submissions. The submission lead has a key role in this endeavour, but in reality a single person does not always have time to review every document in detail. Writers should also review each other's documents to facilitate alignment. For example, the authors of efficacy, safety, and pharmacology summaries should review the corresponding sections of the CO. Ensuring consistency of safety messaging between CSRs, SCS, CO, and RMP is also critical.

#### Challenges are also opportunities

Delivering a submission dossier in record time often seems a daunting task; however, bear in mind that with great challenges come equally great opportunities. Successful accelerated submissions foster a spirit of cooperation and camaraderie that can last for years and benefit the team in many ways. They are also an opportunity to innovate and optimise company processes. Finally, they are an excellent opportunity for professional development for all members of a submission team.

#### 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.

Delivering a submission dossier in record time often seems a daunting task; however, bear in mind that with great challenges come equally great opportunities.

# Upcoming issues of **Medical Writing**



September 2022:

## **A virtual workforce**

Working remotely/working from home has become the norm these days. This issue will focus on various aspects of working from home – the good, the bad, the ugly. We will have articles on the challenges of writing from home, managing teams and also, on how some of us overcome these challenges and enjoy this opportunity.

**Guest Editor: Archana Nagarajan**

The deadline for feature articles has passed.



December 2022:

## **Open science and open pharma**

Open access ensures that the highest quality, peer-reviewed evidence is available to anyone who needs it, anywhere in the world. This issue will focus on how open access and plain language summaries improve transparency, advance medical science and ultimately improve patient care. Focus will also be given to how Open Pharma, a group of pharmaceutical companies and other research funders, alongside healthcare professionals, regulators, patients, publishers and other stakeholders in healthcare, are driving this goal.

**Guest Editors: Martin Delahunty, Tanya Stezhka, and Chris Winchester**

The deadline for feature articles is September 1, 2022.



March 2023:

## **Clinical trials**

Medical writers and communicators are involved in clinical trials, from writing the trial protocol to reporting and publishing the trial results. This issue will focus on our roles, responsibilities, the documents we create, and our audience. Furthermore, we will also cover the regulations and best working practices governing documentations for clinical trials.

**Guest Editors: Raquel Billiones and Ivana Turek**

The deadline for feature articles is December 1, 2022.

### **CONTACT US**



If you have ideas for themes or would like to discuss any other issues, please write to [mew@emwa.org](mailto:mew@emwa.org).



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