

Volume 29 Number 3  
September 2020

# Medical Writing



## European Union regulations

### Also in this issue...

- Ethical challenges in subcontracting professional writing support
- Publication management software for medical writers



EMWA 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).

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# Medical Writing

## European Union regulations

When we first sent out the call for papers for the Autumn 2020 issue of *Medical Writing*, there were only a few reports of a novel coronavirus. Today, of course, COVID-19 is a pandemic. Welcome to the “new normal”, where many of the routines, activities, and work processes we once took for granted have changed significantly or vanished entirely.

Welcome to the “new normal”, where many of the routines, activities, and work processes we once took for granted have changed significantly or vanished entirely.

Indeed, COVID-19 is not a specific topic in this issue, but it has had a subtle effect. This issue includes substantial articles on medical devices. As you may know, the European Council has voted to delay implementing the Medical Device Regulation (MDR) until May 26, 2021, recognising “the need for an increased availability of vitally important medical devices across the EU, and at the same time continues to guarantee patient health and safety until the new legislation becomes applicable”.

However, industry still needs to prepare for this particular new normal as certain associated deadlines have not changed, such as the date for the In Vitro Diagnostic Regulation (IVDR). **Raquel Billiones** and her colleague, **Gauri Jawdekar-Abraham**, compare the regulatory requirements of the IVDR and the MDR. Raquel also explores the impact of delaying the Eudamed launch on clinical investigation disclosure requirements.

**Shalini Dwivedi** and her colleagues provide an overview of regulatory changes in the EU, while **Kelly Goodwin Burri** examines new documentation that will be required under the MDR. These informative articles remind us that medical writers will have a key role in guiding manufacturers as they adapt to changes.

As our adaptation to the new normal inside and outside the workplace continues, **Tiziana von Bruchhausen**

and her colleague, **Sven Schirp**, draw our attention to risk management plans, while **Daniela Kenzelmann Broz** and her colleagues discuss the regulatory background of scientific advice procedures. These features will be of particular interest to medical writers involved in development plans.

Is change always a good thing? **James Monroe** ponders this question as he explores EU software regulations. **Micha Feld** and his colleagues examine the changes to PubMed and their potential effects on regulatory affairs.

As you continue your own adjustments to this new normal and those yet to come, I hope you will find the insights and ideas in this issue helpful. I wish to thank all the authors for taking the time to contribute to this issue. I owe special thanks to the Editorial Board for their invaluable help in editing the articles and bringing the issue together.

**Ana Madani**  
madania@ucmail.uc.edu

### About the Guest Editor

**Ana Madani, MA**, is an active EMWA member and freelance medical writer/editor. She is completing a graduate certificate in Clinical and Translational Research to augment her training in regulatory affairs.



#### GUEST EDITOR



**Ana Madani**  
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# President's Message

What a busy time! The EMWA Professional Development Committee, the Conference Team, and the Executive Committee are working very hard on organising the virtual conference in November, which we hope will be a unique experience for you. The conference will start with an opening ceremony on Wednesday, November 4. On Thursday, November 5, we will have a variety of activities, including talks on predatory publishing, English sessions, how to work efficiently on your business, an exciting sponsored seminar, the freelance business forum, and the option to attend a mindfulness seminar. The symposium day on Friday, November 5, is about Research Integrity & The Medical Communicator: What We Do When No One Is Watching. The following 2 weeks will be packed with workshops. A big thanks to the workshop leaders who all made extra efforts to adapt their workshops for the virtual world!

There was a myriad of decisions to make and so much work behind the scenes. We would not have made it without the help of our EMWA volunteers, who showed their utmost dedication to the cause. Let me take the opportunity to express my deepest gratitude to everybody involved in making the November conference happen, including the Head Office. Remember, all volunteers work without payment and by doing so make it possible to offer trainings and membership at a reasonable price.

We aim to officially honour our volunteers through our social media initiative #EMWATogetherApart, which is supported by our Vice President Carola Krause. We have had around 1000 views per post – please continue to like and share to get our volunteers the visibility they deserve!

Aside of our activities for the November conference, we have successfully launched our virtual Expert Seminar Series (ESS) programme and have planned two more virtual ESS this year, one on Safety/Vigilance reporting for Medical Devices on October 7, and one on Medical Communications later this year. We have also had pilots of virtual round table discussions. Based on the experience gained, we will frame this new format and make it available to all EMWA members.

On another note, I believe that as an organisation of medical communicators, we also have a responsibility in society that goes beyond training. For me, the growing number of

I believe that as an organisation of medical communicators, we also have a responsibility in society that goes beyond training.



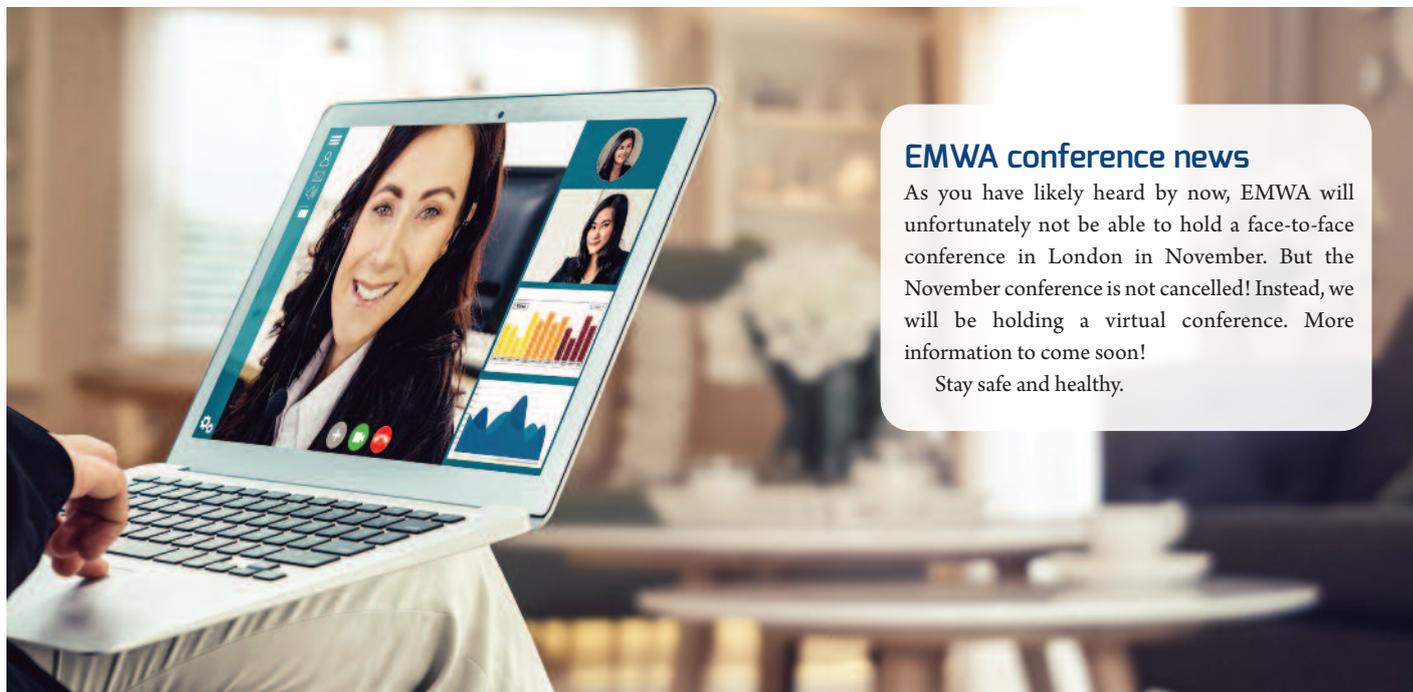
conspiracists and increasing brutality and racism are worrying. We are proud of the diversity, inclusivity, kindness, and helpfulness of our organisation. And by meeting peers from all over the world, of different races, ages, gender, nationalities, religions, cultures, by default, we can overcome prejudices. To clearly state to the outside community that EMWA is a diverse, respectful, and welcoming organisation, we are in the process of developing a code of conduct and rules for etiquette.

In general, acting against misinformation and conspiracies is difficult, and the COVID-19 articles recently retracted from major journals certainly do not help to increase trust in science.

As a reaction, the Medical Communications Special Interest Group has started to work on a position/action statement on scientific peer review that will be developed in partnership with the International Society of Medical Publication Professionals and the American Medical Writers Association. We also aim to strengthen the role of medical writers and communicators with this statement.

Thanks to all of you who are making EMWA an interesting, diverse, and welcoming organisation. I look forward to meeting you virtually in November!

**Beatrix Doerr**



## EMWA conference news

As you have likely heard by now, EMWA will unfortunately not be able to hold a face-to-face conference in London in November. But the November conference is not cancelled! Instead, we will be holding a virtual conference. More information to come soon!

Stay safe and healthy.

## 2020 Symposium: Research Integrity

The annual symposium will be on “Research Integrity”, a topic that is particularly relevant during these times.

The symposium will take place virtually on Friday, November 6th and will be open to both members and non-members.

More details to follow shortly!

### The EMWA member's logo goes live!

Do you want to increase your market value by showing your membership in a professional organisation?

We have released our EMWA member logo, which you can now download from the members-only area of the EMWA website: <https://members.emwa.org/>

Feel free to use it on your website, on social media, and in your email signature!



## #EMWATogetherApart Initiative

In June, EMWA launched the #EMWATogetherApart Initiative on our EMWA social media channels. We aim to provide a digital platform to the medical communications community, where we can share valuable information that can help us during the COVID-19 crisis.

### We honour our volunteers

In addition to our #EMWATogetherApart Initiative, we wish to raise awareness of and give credits to all EMWA volunteers. We aim for a daily post with a THANK YOU message on our social media channels acknowledging EMWA volunteers. We hope to enhance our online visibility and strengthen our community. We

kindly ask you to support your peers by spreading the word, liking, and sharing the provided information under #EMWATogetherApart.

If you are an EMWA volunteer, please send your photograph to [info@emwa.org](mailto:info@emwa.org). We will mention the volunteers in the order we receive the photos.



The EMWA Professional Development Committee (EPDC) is delighted to welcome **Raquel Billiones** as a member of the education committee and **Tania Puvirajesinghe** as a member of the webinar team.

The EPDC is considering options for workshops in light of the cancellation of the face-to-face conference in November and will keep you updated. In the meantime, stay up-to-date with our upcoming webinars:

**October 22, 2020, 14:00 CEST**  
**Sustainability Demystified: An Introduction with Focus on the Healthcare Industry**

**Achim Schneider, PhD**

In 2015, the United Nations set 17 Sustainable Developments Goals (SDGs) as a “universal call to action to end poverty, protect the planet, and ensure that all people enjoy peace and prosperity by 2030”. With less than 10 years to go to achieve these goals, there is an urgent need to understand the principles and science of sustainability and how they fit in our professional and private lives.

This webinar gives an introduction to sustainability, with focus on the healthcare industry. Several examples from the healthcare sector, especially the pharma industry, will be provided. Finally, the objectives of the EMWA sustainability SIG with regard to the SDGs will be presented for discussion.

**December 2020 (exact date to be confirmed)**

**MedCom via video? Veterinary medicine on YouTube as an example of communicating medicine to a lay audience**

**Karim Montasser**, freelance MedComms writer and YouTuber

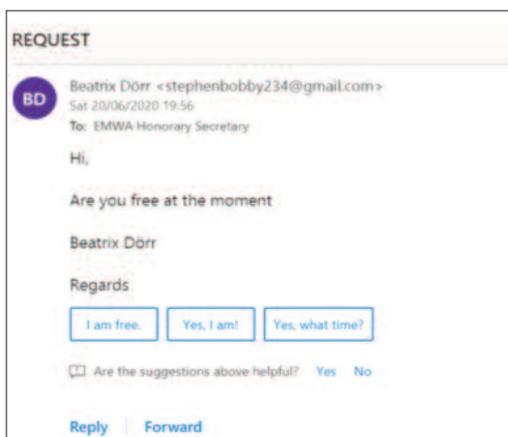
Publishers want it, German politicians press for it, and an ever-growing interested audience is looking for it: Videos that communicate medicine in the form of video abstracts, highly shareable clips or even video essays. In this webinar, we will look at:

- what works on the internet (spoiler: it isn't clickbait)
- which platforms we can use
- what equipment do we need

**WARNING**

We have been made aware of scam emails purporting to come from EMWA or someone connected to EMWA. If you receive anything that looks strange, please report it to the Head Office (info@emwa.org).

Do not respond with any personal or payment information, and do not click on any links. As a tip, always check the email address, as shown in the screenshot of a scam email below:



**Join the new special interest group on sustainability!**

As a professional organisation of medical communicators and healthcare professionals, EMWA can take a more active role in supporting the United Nations Sustainable Development Goals which strive to improve planetary health. Now, following the Executive Committee's approval, the **Sustainability-SIG** (SUS-SIG for short) is looking for your support to develop communication platforms and guidelines on the respectful usage of our digital, human, and planetary resources.

The Sustainability Special Interest Group was launched in May, and on June 25th had its first official meeting! It was attended by eight members (out of twelve interested), and we had a productive conversation.

Learn more about SUS-SIG in this recently published article in *Medical Writing*: <https://journal.emwa.org/the-data-economy/emwa-s-newest-special-interest-group-sustainability-sig/>

Please contact us if you would like to join the SUS-SIG!

**Co-Chairs:**

- **Carola Krause** (vicepresident@emwa.org),
- **Carolina Rojido** (carolinarojido@gmail.com)

**Committee members:**

- **Raquel Billiones**
- **Surayya Taranum**



## Geoff Hall Scholarship: Winners and details of this year's contest

The Geoff Hall Scholarships are given in honour of a 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 based on an essay competition, and the title of last year's essay was 'How would you go about identifying a predatory journal?' This time, the scholarship winners were **Adriana Rocha** and **Petal Smart**.

- **Adriana Rocha** has a degree in Biochemistry from Portugal, which was followed by a PhD in Medical Neurosciences in Germany. After a postdoc in the USA, she decided to leave academic research and transition into industry. She is now a freelance medical writer.
- **Petal Smart** is a veterinary surgeon by training. Over the past five years, she has been a medical/science editor serving primarily non-native English-speaking authors. She has a keen interest in regulatory affairs as they relate to medical devices, both those intended for human use and those intended for veterinary use.

Adriana's and Petal's winning essays were published in the June issue of *Medical Writing*. We wish the winners the very best at the start of their very promising medical writing careers.

For those of you inspired to pick up your laptop and looking for something to fill your time during quarantine, this year's essay title is "**Do you have what it takes to be a medical writer? Discuss three attributes or skills that best qualify one to be a medical writer**".

More details: <https://www.emwa.org/about-us/emwa-awards/geoff-hall-scholarship/>



## Mentorship

No one is born a medical writer. This issue will explore the important role that mentorship plays in the professional development of medical writers.

**Guest Editor: Clare Chang**

The deadline for feature articles is March 8, 2021.

## The June 2021 edition

**Don't miss!**

# The In Vitro Diagnostics Regulation and the role of medical writers

Gauri Jawdekar-Abraham<sup>1</sup>, Raquel Billiones<sup>2</sup>

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## Abstract

Even though in vitro diagnostic medical devices (IVDs) occupy only a very small market segment in the healthcare sector, they have a vital role to play. The importance of diagnostics was strongly underlined during the COVID-19 pandemic. In the EU, IVDs are regulated under the In Vitro Diagnostics Regulation 2017/746 (IVDR), with the planned date of application in May 2022. This article gives an overview of IVDs and the regulatory requirements under the IVDR in comparison to the more well-known Medical Device Regulation 2017/745. Considering the similarities in the regulatory landscape and the document requirements of the two regulations, medical writers well versed in mainstream medical devices have the skills and competencies to support IVDs under the IVDR.

## About IVDs

When a patient visits a doctor, the doctor usually collects blood to evaluate basic blood parameters, e.g., biochemistry, haematology, and biomarkers. As simple as it sounds, basic information obtained from blood samples can provide the physician with general information on the patient's health status. Taken together with a physical examination, the test results are able to guide the physician's treatment decisions. For instance, high C-reactive protein levels are indicative of an infection, or high levels of blood glucose hint towards diabetes. But what is behind these tests? Behind these tests is the in vitro diagnostics industry. It develops and provides test systems, solutions, and rapid tests, and these products are commonly known as in vitro diagnostic medical devices (IVD).

The The In Vitro Diagnostics Regulation 2017/746 (IVDR) defines an IVD as:

*... any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:*

- a. *concerning a physiological or pathological process or state;*
- b. *concerning congenital physical or mental impairments;*
- c. *concerning the predisposition to a medical condition or a disease;*
- d. *to determine the safety and compatibility with potential recipients;*
- e. *to predict treatment response or reactions;*
- f. *to define or monitor therapeutic measures.*<sup>1</sup>

IVD tests are considered to be non-invasive and meant to support the physician in identifying the patient's underlying disease. They are used to analyse human samples such as blood, saliva, urine, or tissue by measuring the concentration of specific substances (e.g., cholesterol, sodium) or detecting the presence or absence of a particular marker (e.g., DNA, RNA, or protein). Figure 1 shows the diversity of IVDs in terms of products, therapeutic areas, applications, and users.<sup>2</sup>

Nowadays, in addition to diagnosing conditions, clinicians also use IVD tests to provide important information for therapy decisions. Screening tests help to stratify patients into drug-responsive vs non-responsive populations based on the expressed biomarker(s), whether protein-, DNA-, or RNA-based to ensure that patients benefit from the appropriate or future therapies. For example, PCR-based IVD tests such as the



OncoBEAM RAS CRC Kit detects rat sarcoma (RAS) gene mutations from plasma of late-stage colorectal cancer patients. It has been shown that patients with colorectal cancer harbouring wild-type RAS genes will benefit from therapeutic approaches that target the epidermal growth factor receptor (EGFR) by antibodies such as cetuximab or panitumumab.<sup>3</sup> However, patients carrying mutations in the RAS genes do not respond to anti-EGFR therapy.

In another example,<sup>4</sup> breast cancer patients overexpressing the human EGFR receptor 2 (HER2) gene will benefit from anti-HER2 therapy while patients overexpressing oestrogen receptor alpha 1 gene (ESR) will benefit from ESR antagonists. Gene expression assays like the Mamma Typer, which is an in vitro molecular

diagnostic test, measures the expression levels of biomarkers in surgical breast cancer samples to guide the right therapy.<sup>4</sup>

The developmental life cycle of the IVD industry is fast-paced compared to that of the pharmaceutical industry. The current COVID-19 pandemic, which has brought the importance of IVD tests to the forefront, shows how suddenly a need for IVD can arise and how fast this need can be fulfilled. Already, a plethora of diagnostic tests have been rapidly developed in a matter of months by several companies. Some have received a CE mark in the EU while others are for research use only.<sup>5</sup>

IVDs that play a central role in companion diagnostics (“devices essential for the safe and effective use of certain medicinal products”<sup>1</sup>) and

personalised medicine need to be co-developed along with their pharmaceutical counterparts. The new IVDR,<sup>1</sup> with a more streamlined approval process similar to the existing pharmaceutical market approval, will provide an opportunity for co-developing these products.

### About the IVDR

Everyone in the healthcare sector would have heard about the MDR which stands for EU Medical Device Regulations 2017/745.<sup>6</sup> Less known but equally important, especially in the current pandemic scenario, is the IVDR that regulates IVDs. IVDR can be considered as the “younger sibling” of the MDR, shorter in length and scheduled for application in May 2022. The two regulations are quite similar in structure,

An IVD is “any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended ... to be used in vitro for the examination of human biological specimens”.

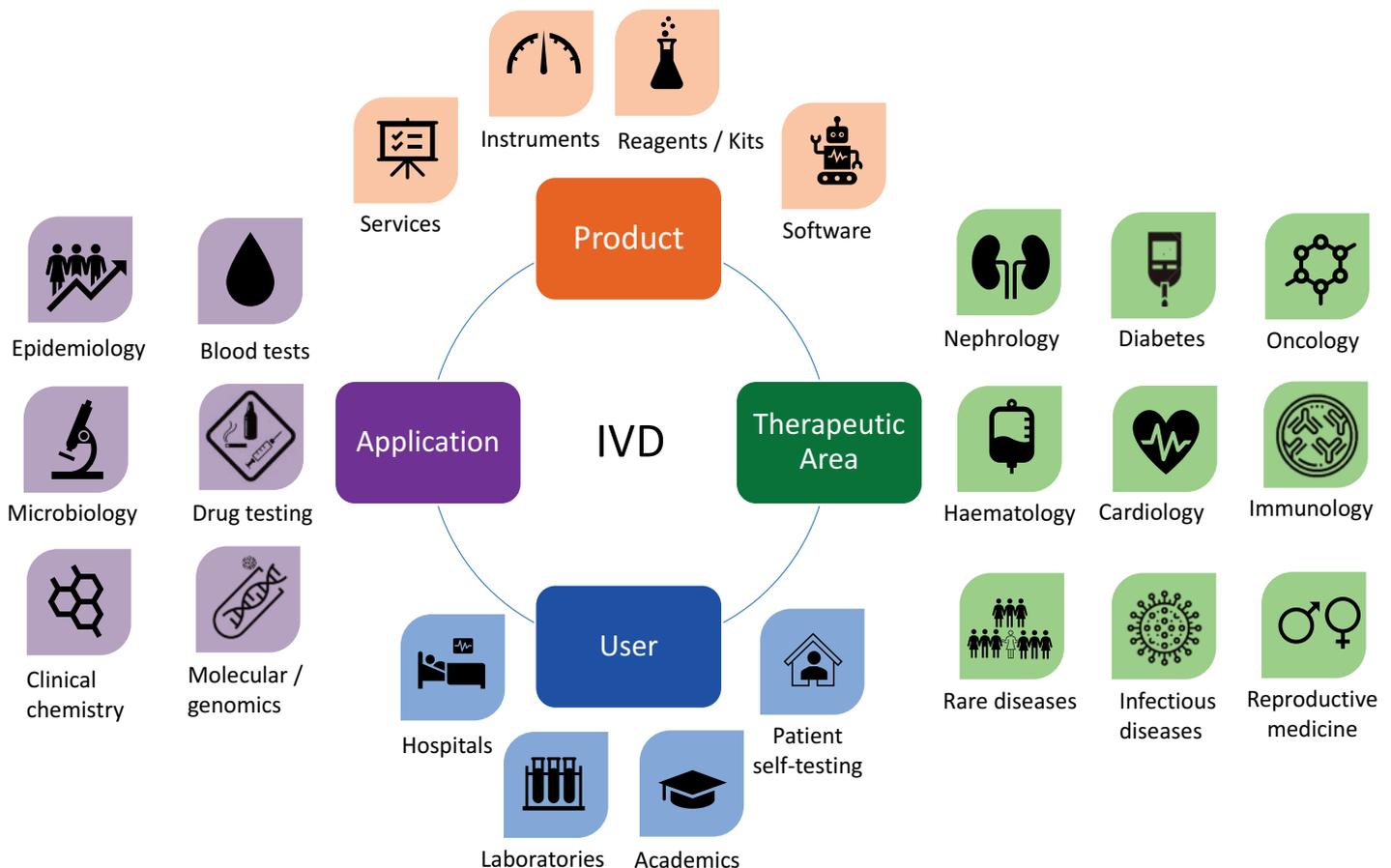


Figure 1. In vitro diagnostic medical devices by product, therapeutic area, application, and user (not an exhaustive list)

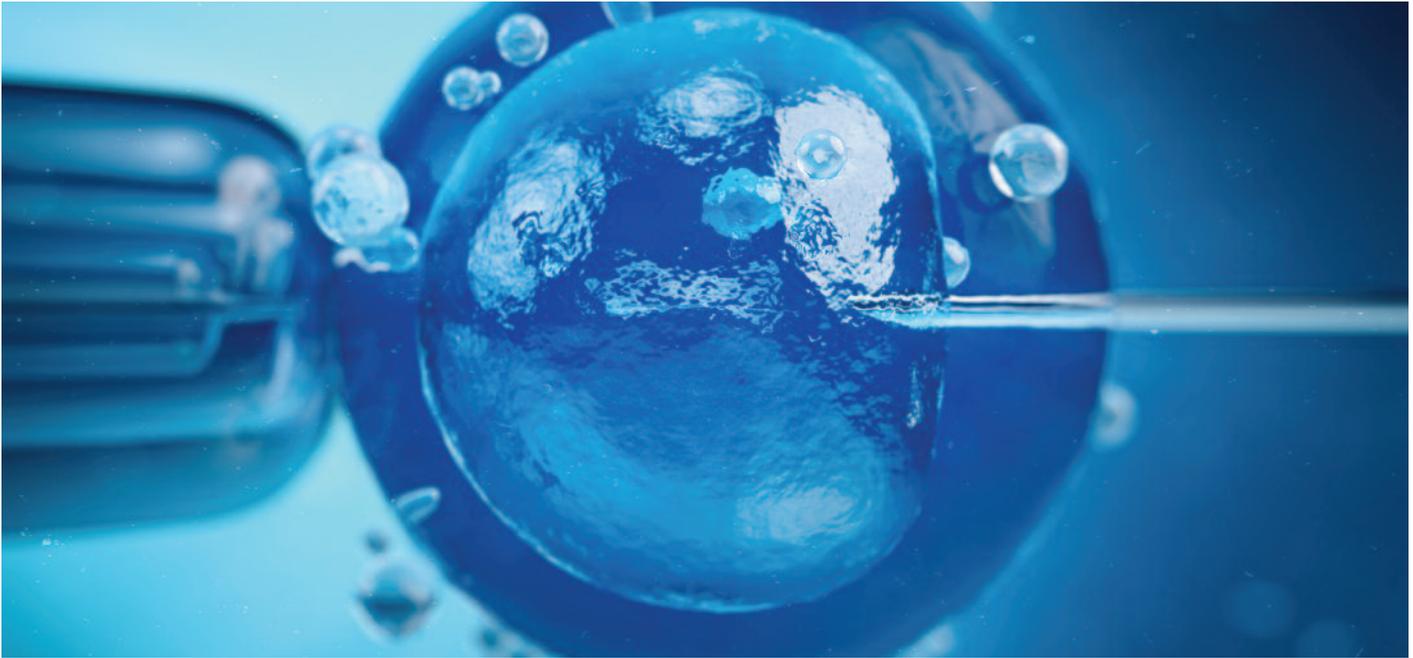
Table 1. Tables of contents of the MDR and the IVDR showing the similarities and key differences

Chapter/ section number	Chapter/section heading in the MDR	Chapter/section heading in the IVDR
Chapter I	Scope and definitions	
Chapter II	Making available on the market and putting into service of devices, obligations of economic operators, reprocessing, CE marking, free movement	Making available on the market and putting into service of devices, obligations of economic operators, reprocessing, CE marking, free movement
Chapter III	Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European database on medical devices	Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European database on medical devices
Chapter IV	Notified bodies	Notified bodies
Chapter V Section 1 Section 2	Classification and conformity assessment • Classification • Conformity assessment	Classification and conformity assessment • Classification • Conformity assessment
Chapter VI	Clinical evaluation and clinical investigations	Clinical evidence, performance evaluation, and performance studies
Chapter VII Section 1 Section 3	Post-market surveillance, vigilance, and market surveillance • Post-market surveillance • Market surveillance	Post-market surveillance, vigilance, and market surveillance • Post-market surveillance • Market surveillance
Chapter VIII	Cooperation between member states, MDCG, expert panels, and laboratories and device registers	Cooperation between member states, MDCG, expert panels, and laboratories and device registers
Chapter IX	Confidentiality, data protection, funding, and penalties	Confidentiality, data protection, funding, and penalties
Chapter X	Final provisions	Final provisions
Annexes	17 Annexes	15 Annexes

Rows highlighted in grey are the key differences. Abbreviation: MDCG, Medical Device Coordination Group

Table 2. Key differences between the MDR and the IVDR Annexes

Category	MDR	IVDR
General safety and performance requirements (Annex I)	Requirements 1 to 23	Requirements 1 to 20
Technical documentation structure (Annex II)	Less granularity	More granularity Details include specimen types, assays, accuracy, sensitivity, specificity, shelf-life, and stability
Device classification rules (Annex VIII)	22 rules that cover non-invasive (4), invasive (4) and active devices (5) and special rules (9)	7 rules
Device classes (Annex VIII)	Class I, IIa, IIb, III	Class A, B, C, D
Clinical evidence	Based on clinical evaluation, post-market clinical follow-up, and clinical investigations (Annexes XIV and XV)	Based on performance evaluation, post-market performance follow-up, and clinical performance studies (Annexes XIII and XIV)



content, and the requirements therein.

Table 1 compares the high-level headings of the two regulations. Table 2 summarises the key differences as detailed in the Annexes of the regulations.

### The role of medical writers in IVDs under the IVDR

On p. 24, our EMWA colleagues expound on the role of medical writers and some of the documents they develop for medical devices under the MDR.

Considering the similarity in the regulatory

landscape for mainstream devices and IVDs, medical writers can also have a key role in complying with documentation requirements in the development and market authorisation of IVDs under the IVDR. The terminologies may differ between mainstream medical devices and IVDs but the principles governing the two sets of products and the requirements for compliance are very similar. Hence, medical writers who are familiar with medical devices and the MDR have skills and competencies that are highly transferrable to IVDs.

For example, Table 1 and Table 2 highlight

the similarities and key differences between the two regulations. Further, Table 3 lists the key documents and their purposes as required under the MDR and the IVDR.

In order to develop these documents, a medical writer needs to draw on knowledge and competencies that include, but are not limited to, scientific writing, good clinical practice, data analysis, safety surveillance, public disclosure, and plain language writing. These are very similar to the skill set that medical writers use in other healthcare sectors such as those dealing with mainstream devices and medicinal products.

**Table 3. Key documents that medical writers may develop as required by the MDR and the IVDR**

Purpose	MDR	IVDR
Clinical evidence	Clinical evaluation plan Clinical evaluation report	Performance evaluation plan Performance evaluation report
Clinical studies	Clinical investigation plan Clinical investigation report Investigator’s brochure Informed consent	Clinical performance study plan Clinical performance study report Investigator’s brochure Informed consent
Post-market surveillance	Post-market surveillance plan Post-market surveillance report Periodic safety update report Post-market clinical follow-up plan Post-market clinical follow-up evaluation report	Post-market surveillance plan Post-market surveillance report Periodic safety update report Post-market performance follow-up plan Post-market performance follow-up evaluation report
Disclosure for the lay public	Clinical investigation results summary understandable by the end user Summary of safety and clinical performance	Clinical investigation results summary understandable by the end user Summary of safety and performance

To develop IVD documents, medical writers need to draw on knowledge and competencies in a variety of areas, including scientific writing, good clinical practice, and data fluency – similar skills used in other healthcare sectors.



In terms of structure and content of these documents, it is expected that the EU Medical Device Coordination Group will eventually provide clear guidance in addition to what is laid out in the IVDR. However, it is important that IVD companies should start the preparatory work to comply with the IVDR requirements as soon as possible. And the role of medical writers should be considered seriously.

## Conclusions

IVDs occupy only a small segment of the healthcare industry. Yet, they play a vital role in healthcare as demonstrated during the COVID-19 pandemic. Medical writing for IVDs is still considered a “niche” and non-mainstream field that requires specialised training and experience. However, it is also clear that the regulatory landscape for mainstream devices and IVD is quite similar. The information provided in this article about IVDs and the IVDR demonstrates that medical writers can easily transition their skills set to support the IVD industry to comply with the IVDR requirements.

## Disclaimers

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

## Conflicts of interest

Both authors are employed in the pharmaceutical industry.

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## Author information

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# Eudamed's delay and its impact on disclosure of clinical investigations under the EU MDR

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## Abstract

The new European Database on Medical Devices (Eudamed) is the platform to be used for the prospective registration of clinical investigations for medical devices under the Medical Device Regulations. However, Eudamed's launch has been delayed till 2022. This article discusses the ramifications and the potential solutions for manufacturers to comply with public disclosure expectations and requirements. Until Eudamed is available, posting on other databases is recommended so manufacturers can meet requirements for clinical investigation transparency and disclosure while sharing clinical investigation information necessary to maintain public trust.

## Introduction

Under the new EU Medical Devices Regulation (MDR) 2017/745, there is an increased requirement to conduct clinical trials (clinical investigations) on certain risk classes of medical devices (Article 62).<sup>1</sup> Conducting clinical investigations also requires transparency and public disclosure of key information and documents.

The key factor in all these public disclosure activities is a fully functional new European

Database on Medical Devices (Eudamed) (Article 73), an electronic database that through its different, yet interoperable modules "will function as a registration system, a collaborative system, a notification system and a dissemination system (open to the public)".<sup>2</sup>

Under the EU MDR, the Eudamed module for clinical investigations will be publicly accessible.<sup>2</sup> The new Eudamed and all its modules were intended to replace the existing Eudamed and planned to be available well in time for the EU MDR date of application (DoA) on May 26, 2020. However, by late 2019, it was

announced that Eudamed will be delayed for at least 2 more years.<sup>2</sup> In March 2020, the European Commission postponed the EU MDR DoA for 1 year due to the COVID-19 pandemic.

## Clinical investigations disclosure requirements under the EU MDR

As defined in Article 73,<sup>1</sup> the registration of clinical investigations and the publication of their results must be on a publicly accessible electronic system as

**Table 1. Disclosure requirements for clinical investigations under the MDR**

Disclosure requirement	Provisions and location in the EU MDR 2017/745 <sup>1</sup>
<b>1. Clinical investigation registration</b>	<ul style="list-style-type: none"><li>• A clinical investigation must be registered in the electronic system for clinical investigations within the Eudamed (Article 73, 1).</li><li>• A unique ID number is assigned for each investigation (Article 70, 1; Article 73, 1a).</li><li>• This information is publicly accessible via Eudamed (Article 73, 3).</li></ul>
<b>2. Clinical investigation application documents</b>	<p>The following documents (Annex XV) must be submitted in the electronic system for clinical investigations within the Eudamed:</p> <ul style="list-style-type: none"><li>• Clinical Investigation Application: Annex XV, Chapter II, 1</li><li>• Clinical Investigation Plan (CIP): Annex XV, Chapter II, 3</li><li>• Investigator's Brochure (IB): Annex XV, Chapter II, 2</li><li>• CIP must describe policy on the publication of results (Annex XV, Chapter II, 3.17).</li><li>• This information is potentially publicly accessible via Eudamed (Article 73, 3).</li></ul>
<b>3. Clinical investigation results reporting and publication</b>	<ul style="list-style-type: none"><li>• A Clinical Investigation Report (CIR) will be prepared within 1 year of the end of the clinical investigation or within 3 months of the early termination or temporary halt, irrespective of the outcome (Article 77, 5).</li><li>• The CIR is accompanied by a summary easily understandable by the intended user (Article 77, 5).</li><li>• Publication of results should be according to legal requirements and recognised ethical principles (Annex XV, Chapter II, 3.17).<ul style="list-style-type: none"><li>• Declaration of Helsinki latest version (Preamble 64)</li><li>• ISO 14155:2011 (Preamble 64), replaced by ISO 14155:2020</li></ul></li><li>• This information is publicly accessible via Eudamed (Article 73, 3).</li></ul>

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part of Eudamed. Table 1 describes these requirements in more detail.

Interestingly, the EU MDR seemed to have anticipated the Eudamed delay under Article 123d:

Until Eudamed is fully functional, the corresponding provisions of Directives 90/385/EEC [Active Implantable Medical Device Directive (AIMDD)] and 93/42/EEC [Medical Device Directive (MDD)] shall continue to apply for the purpose of meeting the obligations laid down in the provisions listed in the first paragraph of this point regarding exchange of information including, and in particular, information regarding vigilance reporting, clinical investigations, registration of devices and economic operators, and certificate notifications.<sup>1</sup>

In the current regulatory setting, what do these delays mean for clinical investigation disclosure requirements? To answer this question, it is helpful to look at some lessons from the pharmaceutical industry.

### Impact of the Eudamed delay

This is not the first time that an EU electronic system has been delayed. The EU Clinical Trials Regulation 536/2014 (EU CTR)<sup>3</sup> entered into force in June 2014. However, the timing of its application also was dependent on having a fully functional EU clinical trials portal and database (collectively known as Clinical Trial Information System [CTIS], the pharmaceutical equivalent to Eudamed) to eventually replace the existing EU Clinical Trials Register and EudraVigilance database. The initial timeframe of the system’s launch was for December 2015. As of September

2020, the CTIS is still not functional and the earliest “go-live” date is planned for 2022.<sup>4</sup>

Like the EU MDR, the CTR has contingency measures to use provisions in the previous legislation, the Directive 2001/20/EC. Currently, the existing EU Clinical Trials Register continues to be used for prospective registration and posting clinical trials results.

Can the same approach be used for medical devices to meet requirement 1 listed in Table 1? The answer is no.

Unlike the existing EU Clinical Trials Register, the existing medical device database under both the MDD and the AIMDD is not designed for clinical investigation disclosure requirements. In its current form, “it is a central repository for information on market surveillance exchanged between national competent authorities and the Commission. Its use is



restricted to national competent authorities, it is not open for consultation and is not publicly accessible.”<sup>2</sup>

Without a fully functional new Eudamed, there are two options for clinical investigation sponsors to resolve the situation:

1. The clinical investigation is prospectively registered in another, existing clinical trial registry, such as one of those listed in the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP).<sup>5</sup>
2. Registration is deferred until the Eudamed is available (retrospective registration).

The current approach among device manufacturers is to proactively prepare all Eudamed requirements, not only those on clinical investigations, which will then be uploaded retrospectively once the Eudamed is operational. However, option 2 does not meet the requirement for prospective registration of clinical study information in the healthcare sector established over the years.

## Why prospective registration of clinical investigations should not be deferred

Transparency in clinical trials is not a novel requirement in the healthcare sector. While transparency began as a voluntary process, over the years it has evolved into a mandatory requirement. However, the European medical device industry has lagged behind in transparency due to a “fragmented” market approval process much different from that of medicinal products.<sup>6,7</sup> The EU MDR aims to change this.

Outside of the MDR, other legislations and guidance documents (as listed below) require clinical investigation disclosure. This forms a sound reasoning as to why manufacturers should consider option 1 to prospectively register their clinical investigations using existing registries.

### Requirements of EU member states

According to EU MDR Article 123d, until there is a fully functional Eudamed, the provisions on clinical investigations under the MDD and



AIMDD continue to apply, such as clinical investigation application and approval and reporting results that follow the requirements of each member state. Unfortunately, these member state requirements are not harmonised across the EU. At a minimum, each member state requires a unique study ID and registration on a public site. The preferred registration platform can vary. See currently available public clinical trial registries below.

### Declaration of Helsinki

The EU MDR refers to the “most recent version” of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. The 2013 version states:

*Article 35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.*

*Article 36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.*<sup>8</sup>

### ISO 14155:2020

The ISO 14155:2020 Clinical Investigation of Medical Devices For Human Subjects – Good Clinical Practice standard was released in July 2020. One key addition to this new version is Section 5.4 Registration in publicly accessible database, which states “In accordance with the Declaration of Helsinki, a description of the

clinical investigation shall be registered in a publicly accessible database before the start of recruitment activities and the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.”<sup>9</sup> It does not specify any preferred registry. The previous version of this ISO standard is cited as a recognized ethical guidance by the EU MDR (Preamble 64).

### International Committee of Medical Journal Editors (ICMJE)

The EU MDR refers to a need for a clear policy for publishing investigation results, placing an increased emphasis on the use of literature data as part of a manufacturer's clinical evaluation process. To publish in reputable biomedical journals, device manufacturers or sponsors must consider the ICMJE's Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.<sup>10</sup> Updated in December 2019, this guidance document requires preregistration of a clinical study in a registry that is a primary register or a data provider of the WHO ICTRP. Approval to conduct a study by a local, regional or national review body is not considered replacement for this prospective registration requirement. In addition, any manuscript based on clinical investigations must be accompanied by a data-sharing statement describing when and how the sponsor should share study documents (e.g., CIP, statistical analysis plan) and datasets (e.g., CIR).

## Currently available public clinical trial registries

In the absence of an operational Eudamed, there are several publicly accessible registries sponsors can use, including those that are part of the WHO ICTRP. Some of these are described below.

### ClinicalTrials.gov

Although not a primary WHO registry, the site is recognized as a WHO data provider. It is by far the largest clinical trial registry globally and covers drugs, biologics, surgical procedures and devices.

### European Clinical Trial Register

This is a primary WHO registry covering interventional clinical trials on medicines. It does not provide information on clinical trials for medical devices and procedures. However, it

does not preclude sponsors of devices, especially those of drug-device combination products, from using this platform for clinical investigation registration.

### Country-specific registries

Two EU countries have country-specific registries as part of the WHO ICTRP, Germany and the Netherlands. Neither registry distinguishes between trials on medicinal products and those on medical devices. They do cross reference to the ICMJE guidance document described above. However, it is important that sponsors and manufacturers consult the national competent authorities in the relevant Member State regarding their preferred register, if any.

### What comes after registration?

Registration of the clinical investigation protocol is the first step. The sponsor also needs to update information in the registry in case of changes and amendments and post results once the investigation is completed. The timing to post investigation results depends on the register and, in the EU, it is generally 1 year after the end of the investigation for adult subjects. The end of an investigation is defined as the date of the last visit of the last subject enrolled in the investigation (Article 77, 2).

Under the MDR, disclosure of results consists of making publicly available the CIR and the lay summary (requirement 3 in Table 1; Article 77, 5) through the Eudamed. It is also possible that other documents such as the CIP and IB (requirement 2) will be disclosed.

It is necessary to keep in mind that any information, data, or document posted publicly, regardless of the register, database or electronic system used, must comply with the requirements for personal data protection under the EU’s General Data Protection Regulation. Hence, the CIR and other documents should be written with data privacy in mind to ensure it is disclosure ready when the Eudamed is ready.

### Conclusion

Eudamed’s delay affects many EU MDR activities. The processes surrounding clinical investigations are especially important for novel and high-risk class devices where generation of clinical data is required. Other guidance documents, including those referenced in the EU MDR, require prospective registration and

posting the results of clinical investigations. Manufacturers will benefit from proactively fulfilling the requirements of clinical investigation transparency and disclosure as data sharing will help maintain public trust in the medical device industry. In addition, data submitted to existing clinical trial registries can easily be reused for Eudamed purposes in 2022.

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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.

### Conflicts of interest

The author is employed in the pharmaceutical industry.

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# Recent and upcoming regulatory changes in the European region: Opportunities for medical writers

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## Abstract

The European regulatory landscape for clinical trials and medical devices is in the midst of major transformation. Older policies are giving way to new regulations that emphasise more harmonised and streamlined processes for document submittal, greater public transparency of documents, and the creation of plain language summaries of clinical trials for easier understanding by the general public. This article provides an overview of important new regulations and policies, including some new guidances regarding research related to the COVID-19 pandemic. This article also discusses opportunities for medical writers working in the context of a new regulatory environment that requires balancing increased public disclosure of information and greater privacy protections for individuals.

## Introduction

In Europe, the conduct of clinical trials has been regulated and harmonised across all EU Member States through the Clinical Trials Directive. Nevertheless, over the past few years, healthcare providers have witnessed major changes to the dynamic EU regulatory landscape. The much

talked-about Clinical Trials Regulation (EU CTR 536/2014) to replace the directive is likely to be implemented in 2023. It is expected to increase the transparency requirements as it will streamline the process of multi-country EU trials through a single portal for all applications. Along with EU CTR 536/2014, the regulatory landscape of devices and drug-device combinations is also changing, as the new EU Medical Device Regulation is scheduled to be implemented in May 2021. The new regulation imposes new requirements, which will require changes in document preparation for devices. This article provides details about such new requirements, changes in preparation of clinical document processes, and associated opportunities for medical writers.

A main objective of the EU Clinical Trials Regulation 536/2014 and other transparency policies is to establish a European database that will serve as a central electronic communication platform for member states, sponsors, investigators, and ethical committees.<sup>1,2</sup> Once EU CTR 536/2014 replaces the directive, there will be new requirements for disclosure of clinical documents at a much earlier point along the timeline. The database will house all relevant clinical information related to a clinical trial – protocol, scientific summary, clinical study report, and safety report, which may have been publicly disclosed as per registered clinical trial application (CTA), results reporting, and EMA Policy 0070 and EMA Policy 0043.<sup>2,3</sup> In addition to this, a plain language summary (PLS) of clinical trial results, following health literacy and numeracy principles, will also need to be posted on the portal, detailing in lay language how the trial was conducted and its results.<sup>4</sup>

By now, medical writers are likely to be familiar with the General Data Protection Regulation (GDPR), enacted in May 2018, which has resulted in major changes to informed consent

processes, data collection, and data reporting.<sup>5</sup> Because of GDPR, trial subjects now have a better control of their data. However, given the current epidemic situation from COVID-19, there are also some special considerations related to privacy, making it especially important that medical writers stay informed as new guidances are issued.

Furthermore, the EU has also witnessed a considerable refurbishment of the regulatory system for medical devices to create a centralised and transparent procedure of assessment that can be implemented across the member states. In recent years, the EU MDR Medical Device Regulation (MDR, 2017/745) and the In Vitro Diagnostic Medical Device Regulation (IVDR, 2017/746) have been enacted.<sup>6</sup> Medical device companies are required to submit clinical documents for approval of new and existing products following these regulations. The following sections present the key changes in the EU regulatory landscape and the importance of

these changes for medical writers.

Given the current epidemic situation from COVID-19, there are some special considerations related to privacy, making it especially important that medical writers stay informed as new guidances are issued.

## EU CTR 536/2014

The EU CTR 536/2014 is based on a comprehensive technology platform known as Clinical Trial Information System (CTIS).<sup>1</sup> CTIS will serve as a portal for clinical trial sponsors to upload trial-related documents for all the key activities throughout the entire lifecycle of a clinical trial, e.g., during submission stage, maintenance of clinical trial documents beginning from the time of decision on authorisation of a trial by EMA and its member states, and through to the study completion stage. Prior to submission on CTIS, sponsors will need to anonymise personally protected data (PPD) and any commercially confidential information in the clinical documents, CTA submissions, CTA / substantial modifications, study results, and ad-hoc reports.



Figure 1 shows the timeframe of EU CTR activities and the clinical study document categories.

EU CTR 536/2014 has also created deferral provisions for the publication of clinical documents based on the clinical trial phase (Table 1). The information like protocol, Investigator brochure, efficacy and safety sections of the investigational medicinal product are allowed for waivers based on categorisation of clinical trial.<sup>2</sup>

However, deferral rules will not be of significant benefit to the sponsors, as other platforms such as the EU Clinical Trial Register and regulations such as EMA Policy 0043 and EMA Policy 0070 will continue to request protocol information, clinical study reports, and clinical and safety modules to be put in the public domain irrespective of the clinical phase.

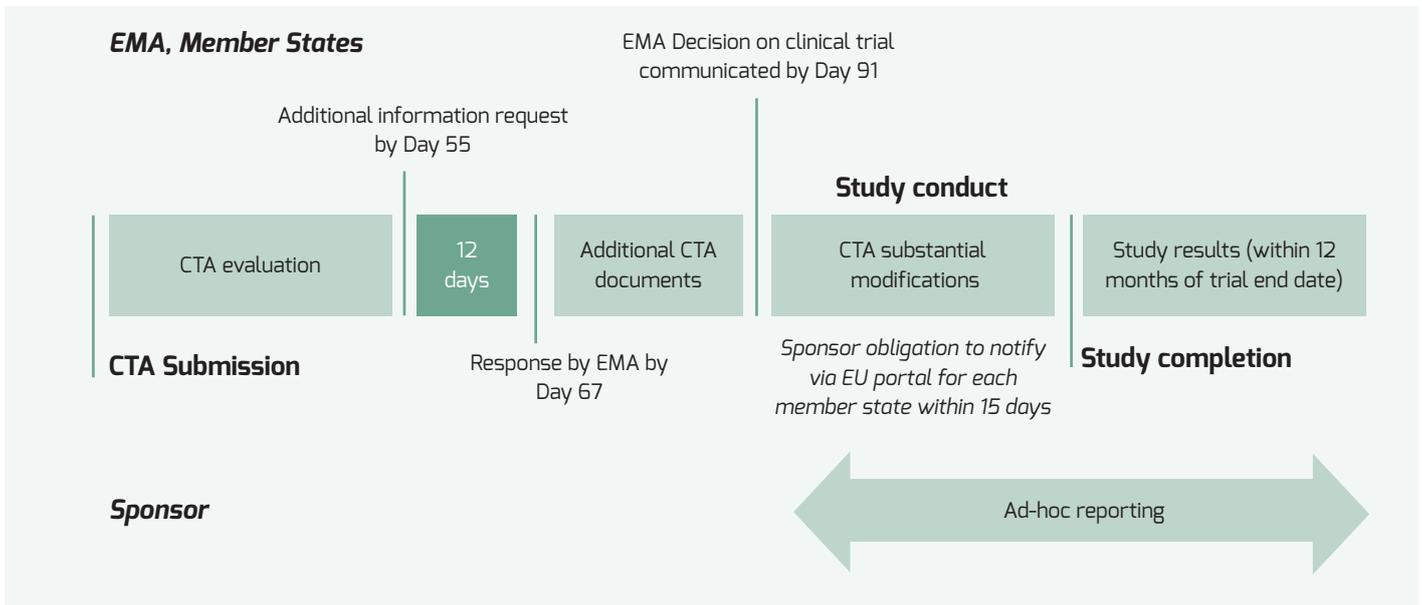
With the requirements to disclose various

clinical documents at regular intervals during a clinical trial, there are a number of points medical writers should consider:

- **The preparation of disclosure-ready clinical documents:** By beginning with the end in mind, writing disclosure-ready clinical documents is imperative in making disclosure activities efficient. Lean, concise writing of these documents will ensure that redaction or anonymisation is only needed in limited sections.
- **The integration of consistent redaction/anonymisation processes:** Sponsors will need to incorporate new processes or streamline existing processes to ensure that redaction/anonymisation strategies are consistent across clinical documents and are performed proactively to meet the new disclosure obligations. Furthermore, it is

imperative to prepare documents in a manner that will require minimal work to anonymise them. To better prepare for the transparency requirements of EU CTR, medical writers should assess PPD and commercially confidential information within the documents and prepare consistent anonymisation. Sponsors will also need to identify any in-scope documents prepared in local languages and require redaction prior to uploading to CTIS. Such documents may necessitate back-translation to English first, to ensure efficient redaction.

- **Anonymisation of clinical documents:** Some sponsors are considering creating a secondary-use CSR using the anonymised dataset. This will eliminate the need to anonymise the CSR for public disclosure. CORE Reference also suggests preparing



CTA submission	CT Substantial modifications	Study results	Ad-hoc reporting
EU Clinical Trial Application Form	Receipt of confirmation of EudraCT number	Interim Results Report	Report of urgent safety measures
EU Active Substance Code Details		CSR Synopsis	
List of countries and status		Clinical Study Report	Report of serious breaches
Legal representative agreement letter	Cover letter	Pop PK and PK/PD reports	
Data Protection		Plain language summary	Inspection reports responses
Recruitment Arrangement	Protocol and substantial modifications	Safety reports	
Certificate of Analysis		EU Clinical trial results registry	Unexpected events
Investigator CVs and other related details		Statistical Analysis Plan	
Facilities details	Scientific advice letters	Case report forms	Study notification reason

Figure 1. A snapshot of EU CTR activities, timeframe and type of documents required



**Table 1. Deferral Rules of EU CTR 536/2014 for clinical documents<sup>2</sup>**

Category	Clinical phase	Deferral term	Deferral allowed for document
Category 1	Phase I, Phase 0, Bioequivalence, Bioavailability	Deferral up to the time of marketing authorisation for Investigational Medicinal Product (IMP) used in the trial or <b>7 years</b> from end of trial, <i>whichever is earlier</i>	Protocol, Subject information sheet, changes to previously public information or documents, Investigator brochure, IMP dossier (IMPD) Safety and Efficacy (S and E) sections
Category 2	Phase II, III	Deferral up to the time of marketing authorisation for IMP used in the trial or <b>5 years</b> from end of trial <i>whichever is earlier</i>	Protocol, Subject information sheet, changes to previously public information or documents, IMPD S and E
Category 3	Phase IV, Low interventional clinical trial	None	Protocol may be deferred for publication till the time of summary results reporting if a suitable justification is provided by sponsor to prove the novelty of trial design and hypothesis

“primary” and “secondary” use CSRs separately.<sup>7</sup>

- **Timely availability of the interim reports and CSRs:** Because clinical trial results

summary will be needed 12 months from the intermediate data analysis date, it is important to finalise the interim data analysis report so that this new disclosure obligation can be

met. As the main source document for preparation of the PLS, the CSR would need to be written as soon as possible after clinical trial completion. For paediatric studies, the

timeline for results' disclosure is even stricter (6 months from global end of trial date). Therefore, to meet the suggested timelines, availability of source documents for disclosure preparation is key.

- **Translation requirements and PLSs:** The master PLS (in English) will need to be translated into local languages for the region where the trial is conducted. The English and translated PLSs will need to be posted on the portal 12 months after the end of trial. To increase efficiency, medical writers may also consider finalising the sections of the PLS that are not data-dependent at the same time of the CSR shell stage, leaving only the data-dependent sections to be completed at the time of CSR finalisation.
- **Clinical trial results summaries format:** It is likely that during the first phase of EU CTR 536/2014 implementation, the format required for the clinical trial results summary for the intermediate analysis and end-of-trial analysis will be similar to a clinical study synopsis or disclosure synopsis. In such a case, the disclosure efforts for preparing the clinical trial results summary in EudraCT will be reduced because the requirement of full data sets may phase out. This may change in the future as new functionalities are added to the EU portal.
- **Developing PLS writing skills:** Medical writers preparing PLSs will need to learn new skills of writing for patients or a non-scientific audience, such as applying health literacy and numeracy principles in PLS preparation. A medical writer will also need to learn to summarise results in a clear, concise, correct, and complete manner, along with considering the appropriate length of the PLS. They may also be required to attain skills to create simple visuals to explain trial results or collaborate with illustrators or designers to create custom visuals/graphics for these documents.

## EMA Policy 0070 and GDPR

EMA Policy 0070 provides for the disclosure of anonymised clinical documents while protecting personal data of trial participants. For compliance, marketing authorisation holders must anonymise PPD by adopting a mix of various anonymisation strategies, followed by a thorough assessment of risk of re-identification.<sup>3</sup> While disclosure of documents is an ethical obligation and clinical trial transparency initiatives have significantly enhanced public access to evidence-

based clinical information, it is important to understand the GDPR implications to prevent any privacy-protection related issues. GDPR came into force on May 25, 2018, replacing the EU Data Protection Directive, with an objective to protect personal information under “right to privacy”, i.e., the rights of individuals to have reasonable control of their data and be better informed about how their data are being used.<sup>6</sup> GDPR applies to the EU, EEA, and any data controller or processor located outside of the EU. Failure to comply with GDPR may lead to monetary penalties and dissolute reputation. To remain compliant with GDPR, data being disclosed should be rendered completely anonymous.

With the evolving EU transparency requirements, pharmaceutical organisations have a greater responsibility for ensuring compliance with GDPR. Although these regulations and policies have been well received by the healthcare industry, they do bring certain challenges:

- While EMA Policy 0070 and EU CTR 536/2014 significantly enhance public access to evidence-based clinical information, the GDPR warrants that personal data are adequately protected. These conflicting regulations lead to underreporting of data (redaction vs transformation techniques), data abuse, privacy risks, and compromise on commercially confidential information.
- Redaction-only methodology decreases data utility, thus different anonymisation strategies must be considered during PPD anonymisation. Re-identification risk assessment should be done by considering three criteria (whether it is still possible to single out an individual, link records for an individual, or infer information about an individual) or a quantitative risk assessment, as recommended by Article 29 Working Party.<sup>8</sup>
- Due to the movement of clinical data across borders, the impact of GDPR on data usage, processing and storage is evident, and pharmaceutical organisations must adapt their processes and systems to maintain GDPR compliance.
- Sponsors also need to ensure consistency

of the publicly disclosed information for scientific integrity.

Because medical writing teams are tasked with activities related to EMA Policy 0043, Policy 0070, and data disclosure, it is imperative that medical writers understand policy requirements and GDPR implications. Medical writers should evaluate collected data for potential risks, be able to categorise information as direct- or quasi-identifiers, and understand anonymisation rules. Organisations should also make resources aware on GDPR requirements to ensure adherence to data privacy policies and to address accidental breaches.

## Guidance during the COVID-19 pandemic

The COVID-19 pandemic has relentlessly affected every aspect of human fraternity across the globe. The healthcare industry is under constant pressure to find an appropriate treatment or vaccine, while responding to rapid challenges related to disruptions in R&D activities, supply chain, and manufacturing.

To help contain the spread of the novel coronavirus, EMA has issued specific guidance on the conduct of clinical trials in EU

member states. In April 2020, the European Data Protection Board issued “Guidelines 03/2020 on the processing of data concerning health for the purpose of scientific research in the context of the COVID-19 outbreak” to reconcile privacy and public safety.<sup>9</sup> It is clear that organisations must be legally obliged to ensure the lawful processing of personal data.

Europe and many countries including India, Singapore, Taiwan, South Korea, Iran, and Israel are tracking their citizens using mobile data through invasive applications<sup>10</sup> (e.g., DiAry and allertaLOM in Italy, GeoTrace in Europe, CovTrack in Romania, Arogya Setu in India, Trace Together in Singapore) for the purpose of medical and administrative interventions. The collected data is anonymised before being shared with health agencies in line with data privacy laws. GDPR Articles 6(e)<sup>11</sup> and 9(g)<sup>12</sup> also have provisions related to the processing of personal data, necessary in the public interest, without consent of individuals during public health

A medical writer will also need to learn to summarise results in a clear, concise, correct, and complete manner, along with considering the appropriate length of the PLS.



emergencies. However, once this situation is over, the previous rules will need to be enforced to ensure judicial use of data and maintain sufficient data protection.

Medical writers should keep themselves abreast of updates made in the guidance and policies by the EMA, while preparing clinical documents. As the COVID-19 crisis has affected site monitoring, patient visits, and data collection activities, amendment to protocols (including informed consents) and trial conduct are inevitable, and these changes need to be properly addressed during results disclosure.

### Medical devices and drug-device combinations

The EU MDR (2017/745) and the IVDR (2017/746) were adopted in April 2017 by the EU Council and the Parliament and entered into force in May 2017.<sup>13,14</sup> The EU MDR did not provide clear regulatory information for devices. Therefore, Article 117 of MDR needed to be amended to provide specific requirements regarding drug-device combinations.<sup>15</sup> This has

changed the legal framework in EU for medical devices, introducing new responsibilities for EMA and for national competent authorities. These regulations replace the three existing directives (93/42/EEC, 98/79/EC, and 90/385/EEC) for medical devices. The MDR has a transition period of 4 years and will fully apply from May 26, 2021. The IVDR has a transition period of 5 years and will fully apply from May 26, 2022.<sup>16</sup>

Article 117 of the MDR introduced a new requirement – inclusion of CE certificate (*Conformité Européene*, which means “European Conformity”) for the device in its marketing application.<sup>15</sup> It requires that the marketing authorisation applications for an integral drug-device combination should include a declaration of conformity, or relevant certificate, issued by a notified body (NB). EMA now has three key roles within MDR – it provides consultation on certain medical devices and drug-device combinations, and opinion on borderline products.<sup>17</sup>

With the MDR, the risk classification for

medical devices categories remains identical compared to the directive for Class I, Class IIa, Class IIb, and Class III. Class III covers the highest risk products. However, MDR reclassifies certain devices and extends the scope to devices that are left out in the directive. New devices included under the scope of MDR are:<sup>18</sup>

- Products without an intended medical purpose
- Devices manufactured utilising non-viable human tissues or cells
- Devices incorporating or consisting of nanomaterial

Manufacturers now need to demonstrate that their medical device meets the revised rules for the classification of MDR. New compliance requirements should be evaluated due to reclassification under the scope of MDR. In the current scenario, many devices will be reclassified to a higher device class, affecting their clinical data requirements and require involvement of NB. A clinical evaluation report, previously based on an analysis of literature,



might require clinical investigation and/or post market clinical follow-up. This will need involvement of medical writers for preparation of clinical investigational plan and report.

The regulation has now created a more patient-friendly environment where transparency, patients' information, and patient preferences are of utmost importance. The regulation mandates the establishment of a comprehensive EU database on medical devices (Eudamed) that will cover the lifecycle of all products available on the EU market. Much of this information will be made publicly available. The following are some of the transparency requirements:

- Registration of clinical investigational studies (Article 73.1); the registration information will be publicly accessible through Eudamed (Article 73.3).
- Publishing of clinical investigational studies results within 1 year of the end of the clinical investigation or within 3 months of the early termination or temporary halt, irrespective of the outcome, including summary of results that can be understood by the intended user (similar to PLSSs)
- Preparation of a summary of safety and clinical performance for all Class III and implantable devices. This summary will need to be updated annually.

- Public disclosure of documents that are part of technical documentation such as the clinical evaluation plan and report, clinical investigation protocols and results, and summary of safety and clinical performance.
- Clinical evaluation application documents will include Clinical Investigation Application (CIP), Clinical Investigation Plan, Investigator's Brochure, CIP must also describe policy on the publication of results.
- A clear policy for publishing investigation results, with an emphasis on evaluating available literature for clinical evaluation process will also be needed. For publication of results, the International Committee of Medical Journal Editors' Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals<sup>19</sup> should be followed.

Dossiers prepared for medical devices include documents similar to those submitted for medicinal drugs, however the content requirements are slightly different, e.g., a clinical evaluation report is equivalent to a CSR written for drugs. Periodic safety update reports, written for drugs, are nonetheless a new requirement for devices according to the MDR.

## Conclusion

Considering the increasing requirements of transparency initiatives in Europe, there are numerous opportunities for medical writers. Several national competent authorities have already updated their processes and systems to be compliant with the regulations. We understand that Eudamed and CTIS both are delayed due to technology-related challenges. However, it is well beyond just an IT-driven initiative, as organisations have to prepare for these changes. As of now, the impact of CTIS on EMA Policy 0070 full data summaries is still being explored. The delay has resulted in some organisations following an observational approach, while many other organisations have started preparing their processes to be ready for the transition. Medical writers should take the opportunity now to organise and plan their writing activities accordingly, given the significant impact of the regulations on internal processes and operational activities.

## Conflict of interest

The authors do not have any conflict of interest.

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# New documents required by the medical device regulation

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## Abstract

This article introduces four documents associated with the new Medical Device Regulation 2017/745: the clinical evaluation plan, post-market clinical follow-up (PMCF) plan and PMCF evaluation report, and the summary of safety and clinical performance. The clinical evaluation plan describes the process that will be used to evaluate the performance and safety of a medical device, eventually resulting in a clinical evaluation report. The PMCF plan describes the procedures to collect post-market clinical data that are presented in the PMCF evaluation report. Finally, the summary of safety and clinical performance presents the relevant clinical evidence related to a medical device to healthcare professionals and patients.

## Introduction

After a 3-year transition period, the Medical Device Regulation (MDR) 2017/745<sup>1</sup> should have come into force in May 2020. With MDR implementation now postponed by one year due to the coronavirus pandemic, medical devices marketed in the EU and European Economic Area will now have to comply with the regulation

by May 2021.<sup>2</sup> For medical writers, implementation of the MDR remains focussed on rethinking clinical evaluation so that it is now a continuous evaluation process with a report – the clinical evaluation report (CER) – produced at regular intervals or when required by new information, and all underpinned by a clinical evaluation plan (CEP). But did you know that the CER and CEP are not the only documents required under MDR? Depending upon the class of device, the following documents may also be necessary: post-market clinical follow-up (PMCF) evaluation plan and report, a summary of safety and clinical performance (SSCP), risk management report, periodic safety update report, and post-market surveillance plan and report.<sup>3</sup> This article introduces four of these new documents – the CEP, PMCF evaluation plan and report, and the SSCP. Figure 1 shows where these four documents fit in the development and post-market phases of a medical device. We also highlight new guidance documents under the MDR and describe where existing MEDDEV guidance documents (implementation guidance issued under the Medical Device Directives, a predecessor to the MDR) are still relevant.

## Clinical evaluation plan

Our first peek into MDR-compliant documentation begins with the CEP. Clinical evaluation

has been defined by the MDR as “a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer.” The CEP is the starting point of the clinical evaluation process for a medical device that results in a CER. The purpose of a CEP is to define the scope of the clinical evaluation and lay out a systematic process by which the clinical evaluation is conducted. Simply put, a CEP should ideally be prepared early during the development of a medical device to identify the clinical data that needs to be generated for market access. It may also be used in the post-market phase to continually assess the need for new clinical evidence.

The MDR requires a well-defined CEP demonstrating that the manufacturer has thorough procedures in place to confirm compliance with the relevant general safety and performance requirements defined in Annex 1 of the regulation. Annex XIV (Part A) of the MDR defines, point-by-point, the required contents that shall be part of a CEP (Box 1). In addition, chapter 7 of the MEDDEV 2.7/1 Revision 4 defines the topics to be considered during the scoping stage of the clinical evaluation process.<sup>4</sup> A well-compiled CEP should have elements from

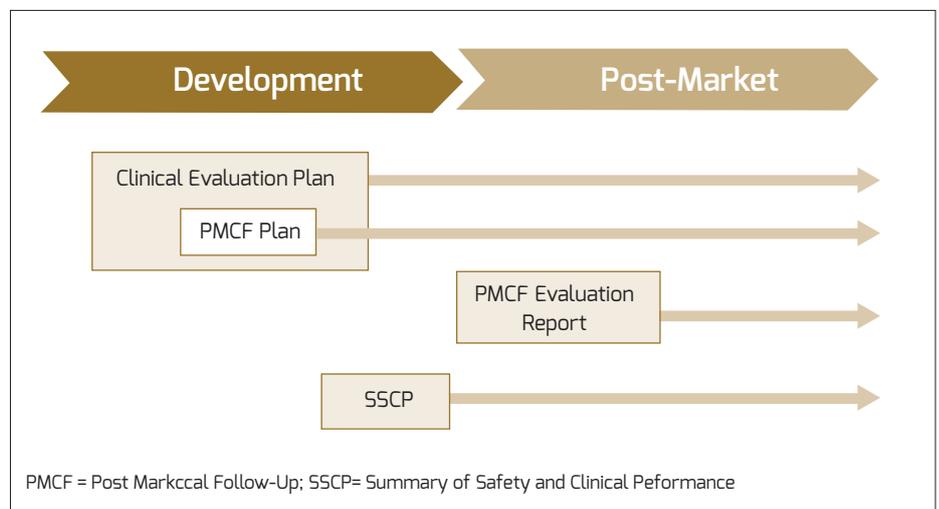


Figure 1. Documents required during medical device development and post-market phases

**Box 1. Required contents of the clinical evaluation plan**

**To plan, continuously conduct and document a clinical evaluation, manufacturers shall establish and update a clinical evaluation plan, which shall include at least:**

- an identification of the general safety and performance requirements that require support from relevant clinical data;
- a specification of the intended purpose of the device;
- a clear specification of intended target groups with clear indications and contraindications;
- a detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters;
- a specification of methods to be used for examination of qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side-effects;
- an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device;
- an indication how benefit-risk issues relating to specific components such as the use of pharmaceutical, non-viable animal or human tissues, are to be addressed; and
- 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 with an indication of milestones and a description of potential acceptance criteria.

Source: MDR 2017/745 Annex XIV Part A<sup>1</sup>

With MDR implementation now postponed by one year due to the coronavirus pandemic, medical devices marketed in the EU and European Economic Area will now have to comply with the regulation by May 2021.





both the MDR and the MEDDEV guidelines.

While the European Commission, in the form of the Medical Device Coordination Group (MDCG), provides a range of guidance documents to assist stakeholders in implementing the medical device regulations (including the other materials discussed in this article), it lacks guidance on preparing a CEP. Moreover, this topic is still not part of the planned MDCG guidance documents.

The CEP is an important document for the different parties involved in the product life cycle. These include, among others, the manufacturer, the Notified Body and their experts, the Competent Authorities in Europe, and regulators in general (for example, delegates of the European Commission when they carry out a joint audit of the Notified Body). The CEP may also be used in submissions to other health authorities abroad that rely on the CE mark technical documentation, e.g., for the Australian regulatory submission pathway or some countries in Latin America.

Writing a CEP is a team effort, requiring information that comes from multiple sources.

**The CEP is a living document that needs to be updated proactively on a regular basis.**

In addition to medical writers, the teams, departments, or professionals involved in creating a CEP primarily include people from the clinical and medical affairs team, the regulatory affairs team, the vigilance/post-market surveillance team such as device safety specialists, the R&D team such as product development or maintenance engineers, the marketing team such as product managers, and the clinical experts. The medical writer will need input from documents, including parts of the design history file, instructions for use (IFU), and other accompanying documents, such as surgical techniques or product brochures, verification and validation plans, post-market surveillance and PMCF plans, clinical investigation protocols (for carrying out clinical investigations if needed), and the risk management plan.

The CEP is a living document that needs to be updated proactively on a regular basis. The MDR and MEDDEV do not provide explicit guidance on the frequency of CEP updates, but the document should be reviewed during the CER update process to determine if any changes are needed.

To summarise, a CEP is a scoping document that allows the manufacturer to put in place the necessary plans required to evaluate the performance and safety of their medical device. It should include elements defined by both the MDR and the MEDDEV. Moreover, the CEP must be updated regularly by the manufacturer. Eventually, it will result in a CER.

### **PMCF evaluation plan and report**

Post-Market Clinical Follow-Up (PMCF) is part of post-market surveillance and was required under the Medical Devices Directive (MDD) amendment 2007/47/EC<sup>5</sup> with guidance provided in MEDDEV 2.12/2 rev. 2.<sup>6</sup> PMCF is the process of collecting clinical data on a CE-marked device to confirm clinical performance and safety during the device's expected lifetime.<sup>3</sup> It is also a means of determining the acceptability of identified risks and of detecting emerging risks by gathering long term data from a larger patient population than is possible during device development. The PMCF plan describes the methods and procedures the manufacturer will use to collect clinical data for the CE-marked device.<sup>6</sup> These data are presented in the PMCF

**Box 2. Required contents of the PMCF Plan**

**The PMCF plan shall specify methods and procedures for proactively collecting and evaluating clinical data with the aim of:**

- a. the general methods and procedures of the PMCF to be applied, such as the gathering of clinical experience gained, feedback from users, screening of scientific literature and other sources of clinical data;
- b. the specific methods and procedures of PMCF to be applied, such as evaluation of suitable registers or PMCF studies;
- c. a rationale for the appropriateness of the methods and procedures referred to in points (a) and (b);
- d. a reference to the relevant parts of the clinical evaluation report referred to in Section 4 and to the risk management referred to in Section 3 of Annex I (of the MDR);
- e. the specific objectives to be addressed by the PMCF;
- f. an evaluation of the clinical data relating to equivalent or similar devices;
- g. reference to any relevant common specifications, harmonised standards when used by the manufacturer, and relevant guidance on PMCF; and
- h. a detailed and adequately justified time schedule for PMCF activities (e.g., analysis of PMCF data and reporting) to be undertaken by the manufacturer.

Source: MDR 2017/745 Annex XIV Part B<sup>1</sup>

evaluation report, which contributes to the clinical evaluation of the device and is part of the CER and the technical documentation.<sup>1</sup>

A PMCF plan and report were required under MDD; the clinical requirements have not changed with MDR, but the procedure for demonstrating compliance has changed.<sup>3</sup> MEDDEV 2.12/2 gives guidance stating that “the requirement for PMCF studies is based on the identification of possible residual risks and/or unclarity on long term clinical performance that may impact the benefit/risk ratio” and cites examples of when a PMCF study might be justified.<sup>6</sup> But the MEDDEV guidance is not legally binding, and non-compliance with a MEDDEV guidance could not be a reason for non-compliance with the MDD.<sup>3</sup> Thus, manufacturers could decide that a PMCF study was not necessary and that their approach to PMCF was acceptable. MDR now makes it clear that PMCF is not an option but a requirement.

Annex XIV part B of the MDR specifies the methods and procedures for proactively collecting and evaluating clinical data with the aims of:

- Confirming the safety and performance of the device throughout its expected lifetime

- Identifying previously unknown side-effects and monitoring identified side effects and contraindications
- Identifying and analysing emergent risks
- Ensuring the continued acceptability of the benefit-risk ratio
- Identifying possible systematic misuse or off-label use of the device

The Annex also specifies the required contents of the PMCF plan (Box 2). The MDCG has recently published additional guidance in the form of templates for both the PMCF plan and the PMCF evaluation report.<sup>7,8</sup> The templates lay out in more detail the required content and structure expected for each of these documents to describe, among other aspects, the activities undertaken related to PMCF and the results of those activities, an evaluation of clinical data relating to equivalent or similar devices, and for the report, a summary of the impact of the results on the technical documentation.

Medical writers are increasingly involved in writing PMCF plans and, in due course, PMCF

evaluation reports. Writers work together with clinical operations who oversee clinical investigations and device registries, post-market surveillance, regulatory, and quality assurance groups in order to prepare PMCF plans and reports.

The PMCF plan is prepared during the development of the medical device together with the CEP (Figure 1). It will be summarised in the initial CER and is part of the technical documentation submitted for conformity assessment. The PMCF plan will be scrutinised by the Notified Body, who will determine whether there are already sufficient clinical data and if the proposed PMCF plan will address any identified gaps in clinical evidence. Once the device is CE-marked, the PMCF findings are analysed and presented in the PMCF evaluation report. This report is prepared annually for class III and implantable devices, every two to five years or as required for class IIa and IIb devices, and as needed for class I medical devices.<sup>3</sup> The PMCF report should be produced in time for inclusion in an updated CER. The PMCF plan should be reviewed and updated as part of the clinical evaluation of a medical device.

To summarise, the PMCF plan and evaluation report are part of post-market surveillance. The PMCF plan describes the methods and procedures to be used to collect clinical data for the CE-marked device, which are then analysed and presented in the evaluation report.

### Summary of safety and clinical performance

The SSCP is an entirely new requirement under MDR. According to Article 32 of the MDR manufacturers shall prepare an SSCP for implantable devices and class III devices, other than custom-made or investigational devices. The SSCP should provide an objective and balanced summary of the clinical evaluation results of all the available clinical data related to the device in question, whether favourable, unfavourable, or inconclusive, among other information. It is not intended to provide general advice on diagnosis or treatment of a medical condition, replace the device’s IFU, or replace mandatory information on patient implant cards or any other mandatory document.<sup>9</sup> The required content of the SSCP is

Medical writers are increasingly involved in writing PMCF plans and, in due course, PMCF evaluation reports.

### Box 3. Required contents of the summary of safety and clinical performance

**The summary of safety and clinical performance shall include at least the following aspects:**

- a. the identification of the device and the manufacturer;
- b. the intended purpose of the device and any indications, contraindications and target populations;
- c. a comprehensive description of the device;
- d. possible diagnostic or therapeutic alternatives;
- e. reference to any harmonised standards and Common Specifications applied;
- f. the summary of the clinical evaluation, and relevant information on post-market clinical follow-up;
- g. suggested profile and training for users;
- h. information on any residual risks and any undesirable effects, warnings and precautions.

Source: MDR 2017/745 Article 32(2)<sup>1</sup>

summarised in Box 3. In addition to the contents defined by MDR Article 32, medical writers can refer to the MDCG guidance document for direction on how to prepare the SSCP and the minimum content required.<sup>9</sup>

The SSCP is written specifically for the end users of a medical device, including both healthcare professionals and, if relevant, patients. The manufacturer has the responsibility of deciding whether content for patients is needed. Information written for patients is mandatory for implantable devices for which patients will be given implant cards and class III devices that are intended to be used directly by patients but may not be needed for exempt devices such as sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips, and connectors. If the SSCP contains information for both healthcare professionals and patients, the document should incorporate separate and clearly distinguishable sections tailored to each audience. The SSCP will be publicly available on the European database on medical devices (Eudamed) when this is ready for use (expected in May 2022). Additionally, the device IFU needs to contain all information required to find the SSCP on Eudamed, including the URL to the Eudamed public website (once available) and linked to the Basic UDI-DI, the unique identification number for the device.

The team involved in writing an SSCP relies on the quality of input documents. The writer may need inputs from the medical advisor/clinical expert, medical affairs, clinical research, and regulatory affairs teams. Because the SSCP is

in the public domain, it may also be subject to an extensive review and require approvals from legal, trademark, and communications or marketing departments. Ultimately, Notified Bodies are the final reviewers of the document, as they need to validate it before it is finalised and published on Eudamed. The source of information required to write the SSCP comes from the technical documentation of the device, which includes design verification/validation reports, risk management report/file, the CER, post-market surveillance and PMCF plans and report, and the IFU. The CER is the most important input document for the SSCP. The PMCF plan and report may also be an input document for the SSCP, although this content is often also addressed in the CER.

The SSCP needs to be ready for product launch and updated whenever there are any updates to the PMCF evaluation report, the periodic safety update report, and the CER. The final SSCP must be translated following the specific member state requirements for the IFU,<sup>9</sup> depending on whether the information is required for healthcare professionals or patients or both. If the selection of European languages for the SSCP does not include English, an English translation should be submitted for healthcare professionals in all member states. There should be one SSCP for each language and the language translation should be validated by the Notified Body.

To summarise, the SSCP is intended to provide a summary of the clinical evidence related to the safety and clinical performance of

a medical device to healthcare professionals and, if relevant, patients. The document will provide a publicly available source of information for intended users validated by the Notified Bodies.

## Conclusions

The MDR introduces several new documentation requirements for medical devices. Additional detailed guidance on how to incorporate the MDR requirements into specific documents is still being developed by the MDCG with templates currently available for the PMCF plan, PMCF evaluation report, and the SSCP. The postponement of MDR implementation gives the medical device writer additional time to become familiar with the new document requirements and upgrade the skills and expertise required.

## Disclaimers

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

## Conflicts of interest

The authors declare no conflicts of interest.

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# Risk management plans in the EU: Managing safety concerns

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## Abstract

The preparation of pharmacovigilance documents is related to ongoing activities during the life cycle of a medicinal product and encompasses crucial processes beyond writing: strategic planning and interdisciplinary work in the context of submissions, definition of the safety concerns of a medicinal product, alignment with the key messages in marketing authorisation application dossiers, and interactions with health authorities during assessment.

Safety concerns are a set of important risks and missing information that are defined during clinical development and carried forward into the post-marketing phase. The risk management plan (RMP) describes the system managing the safety concerns. Although safety concerns are well defined in the EU Good Pharmacovigilance Practice (GVP) guidance, in practice, they are nonetheless frequently the subject of interactions with health authorities. For the RMP, the revised definition of safety concerns in GVP Module V revision 2 has implications not only for other pharmacovigilance documents, but also for the management of safety concerns worldwide.

In the world of pharmacovigilance (PV), the concept of safety concerns is not new. Safety concerns, defined as important identified risks, important potential risks, and missing information (see Table 1), had already played a significant role in Volume 9a of The Rules Governing Medicinal Products<sup>1</sup> in the European Union, the guideline preceding the current European legislation, the Guidelines on Good Pharmacovigilance Practice (GVP).<sup>2</sup> However, before 2012, the impact of safety concerns on the writing and management of pharmacovigilance documents was very low.

This changed in 2011 with the introduction of the Development Safety Update Report (DSUR)<sup>3</sup> and the implementation of the GVP modules on the Risk Management Plan (RMP)<sup>4</sup> and the Periodic Safety Update Report<sup>5</sup> (PSUR, also: Periodic Benefit Risk Evaluation Report, PBRER) in 2012.

In all three reports, safety concerns play a central role and have become major drivers of the content and resources associated with writing these documents. If the DSUR, RMP, and PSUR are seen as three chapters in the life cycle of a medicinal product, one could consider the safety concerns as the “main characters” of the story told in these PV documents (Figure 1).

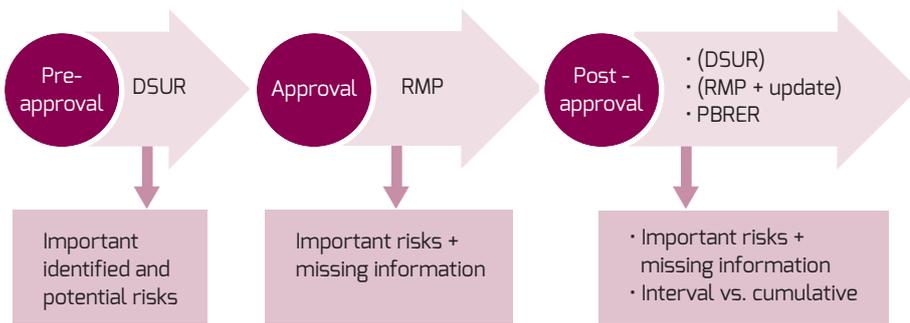
Once the first investigational clinical trial of a clinical development programme is approved anywhere in the world, clinical trial sponsors are obliged to write an annual DSUR, the “first chapter” in the life cycle of a medicinal product. The objective of the DSUR is to provide a single concise common report on the periodic analysis of clinical trial safety for an investigational drug. Focusing on significant safety findings, the DSUR introduces the concept of important identified and potential risks defined as “an identified risk or potential risk that could have an impact on the benefit-risk balance of the product or have implications for public health”.<sup>3</sup> In the DSUR, particular emphasis is placed each year on interpretation of data related to newly identified safety concerns, or significant new information related to previously identified safety concerns. As more and more safety data are produced and evaluated over time, some safety concerns may be excluded and others might be added to the DSUR, so that there will likely be a set of important identified and potential risks at the time when the company is starting to prepare the marketing authorisation application.

The “second chapter” in the life cycle of a medicinal product is the RMP, which is a mandatory part of the application for marketing

**Table 1. Definition of safety concerns**

Identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest
Potential risk	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed
Important identified risk and important potential risk	An identified risk or potential risk that could have an impact on the benefit-risk balance of the product or have implications for public health
Missing information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant
Safety concern	An important identified risk, an important potential risk, or missing information

Data source: GVP Annex I Rev 4



**Figure 1. Life cycle of the safety concerns**

Abbreviations: DSUR, Development Safety Update Report; RMP, Risk Management Plan; PBRER, Periodic Benefit-Risk Evaluation Report.

authorisation in the EU and serves as a detailed description of the risk management system. GVP dedicates Module V to the topic of the RMP<sup>4</sup> and describes the risk management system as “a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of

those activities and interventions”. In its first version (revision 1),<sup>6</sup> GVP Module V introduces the RMP in a modular structure, with Module SVII focusing exclusively on the evaluation of the safety concerns. Unless new important identified or potential risks are defined based on the analysis of pooled clinical trial data during preparation of the first RMP, they will likely be

copied from the DSUR, probably adding “missing information” to the list of safety concerns, based on the current definition. In addition to the evaluation of the safety concerns, authors of the RMP are asked to present detailed PV activities to further evaluate the safety concerns and to minimise these risks, as well as to provide measures to evaluate the effectiveness of additional risk minimisation. As part of the RMP, Part VI is prepared, presenting the safety concerns in plain language so that the public can later understand the medicinal product’s safety concerns and the associated risk management system.

Once the submission package is ready and submitted to the EMA, the RMP is thoroughly reviewed by assessors who take a critical look at the safety concerns and associated PV activities and risk minimisation measures. The assessors commonly request changes to the list of the safety concerns or other sections. As a result, there can be multiple updates to the RMP before the medicinal product is finally approved.

After successful registration in the EU, it is

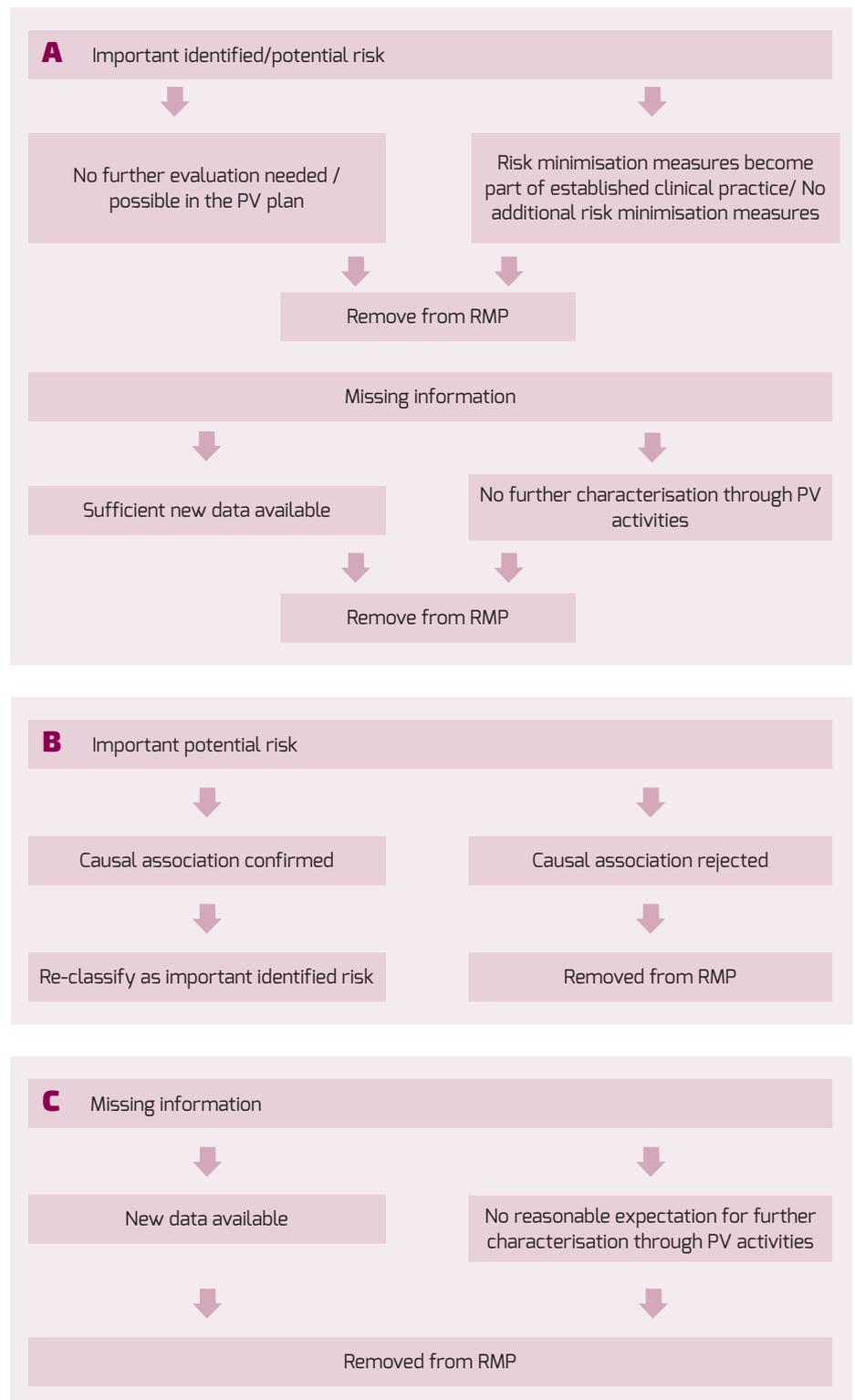


time for the “third chapter” in the life cycle of a medicinal product to begin. The PSUR, newly designed with the implementation of GVP Module VII,<sup>5</sup> presents the post-marketing evaluation of the safety concerns in section 16. When the RMP and PSUR GVP modules were introduced in 2012, the modular structure of the RMP allowed for an easy transfer of RMP Module SVII to PSUR section 16, since the list of safety concerns was identical. For many products, this list grew over time, often with each PSUR assessment, leading to products with more than 20 safety concerns. Many of these important risks were managed by routine activities, e.g., a warning statement in the product information with no additional pharmacovigilance activities. Over the years, when there was no reason to update the RMP, RMPs were left with outdated data, because only the PSUR presents periodic and cumulative up-to date evaluations of the safety concerns.

Revision 2 of GVP Module V,<sup>4</sup> implemented in 2017, introduced a new RMP template and updated definitions for safety concerns, aimed at reducing the “laundry list” of safety concerns. The new RMP should be designed to focus on those risks that have an impact on the benefit-risk balance of the product and would usually warrant further evaluation as part of the PV plan and/or additional risk minimisation activities. A scientific rationale is now needed for inclusion of missing information in the RMP (Figure 2). As of March 2018, the use of the revised RMP format became mandatory for all RMP submissions. The guidance on the format was updated in October 2018.<sup>7</sup>

As can be expected, revision 2 of GVP Module V led to a well-received reduction of safety concerns presented in the RMP, also reducing the workload of writing, updating, and assessing RMPs. Some marketing authorisation holders (MAHs) were asked by assessors to revise the list of safety concerns in accordance with revision 2, others proactively proposed to remove safety concerns, e.g., when submitting the PSUR. Currently, the feedback received from the EMA is inconsistent: sometimes safety concerns are removed without hesitation, whereas it is requested that others remain in the RMP, although there are no additional PV or risk minimisation activities.

The revised definition of safety concerns introduced in revision 2 does not apply to the PSUR. Safety concerns in the PSUR are still defined according to GVP – Annex I,<sup>8</sup> i.e., risks



**Figure 2. Changes over time in the list of safety concerns according to GVP Module V revision 2.** When knowledge on the product’s safety increases, and PV activities or additional risk minimisation measures are no longer needed, safety concerns might be removed or re-classified in the RMP. Lack of data over time might be a reason for removal of important potential risks and missing information topics. Abbreviations: PV, pharmacovigilance; RMP, Risk Management Plan.

that affect the benefit-risk balance. Simply removing an important risk from the RMP does not justify removing it from the PSUR.

Revision 2 of GVP Module V introduced a new way to categorise and evaluate important risks: having defined the important risks as those that (could) have an impact on the benefit-risk profile of a medicinal product, there may now be a subset that is considered “more important”. For example, “more important” risks are those that need further characterisation through additional PV activities or management by additional risk minimisation measures.

The PSUR guidance has not been updated since GVP Module V revision 2. Therefore, there is an apparent disconnect between the criteria that apply to either document and no clear guidance on how to manage safety concerns between the PSUR and RMP.

If an important identified risk is removed from the RMP, the EMA might request to keep this risk in the PSUR, either as a monitoring topic or in section 16 as an important risk. In some cases, it could be sufficient to monitor removed risks through routine PV activities, without including them in the PSUR. Should any new relevant safety findings emerge over time, which would trigger re-evaluation and re-categorisation of these risks, the RMP would subsequently be updated. Currently, there is no clear guidance on how to proceed with the PSUR when safety concerns are removed from the RMP.

The situation becomes more complex when a MAH markets a medicinal product also outside the EU. While the RMP is considered as a regional (EU) document, the PSUR is a global report, accepted by health authorities around the world. The RMP refers to the safety concerns approved by a health authority and describes the risk minimisation measures included in the local product information (the Summary of Product Characteristics). For this reason, it is not sufficient to transfer information from Module SVII of the RMP to section 16 of the PSUR. The PSUR should also include safety concerns

defined by health authorities outside the EU. In some situations, various countries or regions may have a certain risk in the list of the safety concerns, but the categorisation might differ (e.g., identified vs potential). Such deviations need to be taken into consideration and appropriately described in the PSUR. To add a further layer of complexity, MAHs might have their own list of safety concerns that represents their view of the product’s benefit-risk profile worldwide. Companies need to create strategies on how to manage the safety concerns across regional and global PV documents.

There is some ICH<sup>9</sup> and EU<sup>10</sup> guidance on how to present regional deviations in the list of safety concerns in PSURs. However, there is no unambiguous guidance on how to categorise safety concerns in the PSUR that have been removed from the RMP: these could be handled as monitoring topics, risks not considered important, or as important risks. What is the correct perspective of data presentation and risk categorisation for global PSURs: should the EU list of safety concerns really be used as a minimum for PSURs, as indicated in the explanatory notes to the PSUR guidance GVP Module VII?<sup>10</sup>

All of these questions are not just theoretical, almost philosophical brainstorming, but represent real situations the MAHs face in post-marketing based on their interactions with health

authorities, subsequent PSUR submissions, and possible RMP updates.

Many RMPs still include safety concerns that do not strictly meet the approach presented in GVP Module V revision 2. This poses issues in particular for



companies that have to create RMPs for generic products. MAHs and assessors might need further training to ensure that only risks with additional PV or risk minimisation activities are included.

When revision 2 of GVP Module V was issued, the EMA announced an upcoming update of the PSUR guidance (GVP Module VII). Unfortunately, this update was put on hold. In the meantime, MAHs and regulatory agencies have been in active dialogue regarding the re-categorisation of safety concerns and the interactions between RMPs and PSURs. The experience gained so far after revision 2 of GVP Module V should provide a good basis for a revision of the PSUR guidance, which would be helpful for all those involved in preparing and assessing safety documents.

All of these questions are not just theoretical, almost philosophical brainstorming, but represent real situations the MAHs face in post-marketing based on their interactions with health authorities, subsequent PSUR submissions, and possible RMP updates.



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## Disclaimers

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

## Conflicts of interest

The authors declare no conflicts of interest.

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November 6, 2020



# Scientific advice procedures in the EU

## – an overview of the regulatory background

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### Abstract

The prerequisite for obtaining marketing authorisation is an appropriate and robust data package that demonstrates a medicinal product's quality and its efficacy and safety in the proposed indication. Pharmaceutical companies can face regulatory challenges during product development, especially in case of novel treatment modalities, new substances, or rare indications. To support the generation of the appropriate evidence and accelerate patient access to novel treatments, both the EMA and National Competent Authorities offer scientific advice, which allows companies to obtain guidance from a panel of experts regarding quality, non-clinical, clinical, or other aspects of their development strategy. This review provides regulatory background information on the scientific advice procedure in the EU for medical writers, who may become involved in the preparation of the pertaining briefing package.

### Background on scientific advice procedures

#### Legal basis and scope

Developing new medicines is a lengthy and complex process, with an estimated attrition ratio of 10.000:1 and overall costs that can exceed one billion US dollar.<sup>1,2</sup> One of EMA's tasks is "advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety, and efficacy of medicinal products" according to Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council.<sup>3</sup> Accordingly, the EU scientific advice (SA) procedure has been established by the EMA to support the timely and sound development of high-quality, effective, and safe medicines, for the benefit of patients.<sup>1,4</sup> Since the establishment of the procedure in 1996, the number of SA requests has steadily increased (Figure 1).<sup>5-11</sup>

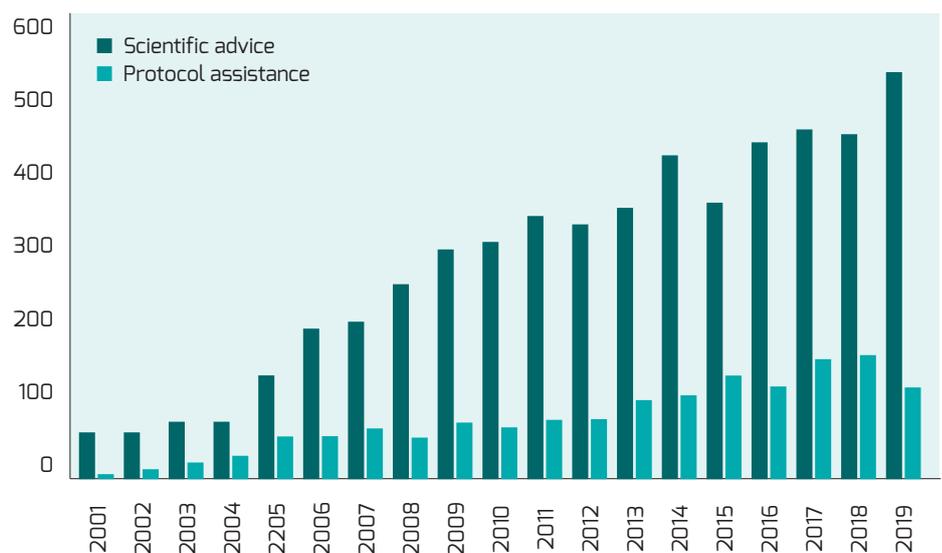


Figure 1. Numbers of scientific advice and protocol assistance requests to the EMA

Source: EMA annual reports 2001, 2004, 2007, 2010, 2013, 2018 and 2019<sup>5-11</sup>



SA may be requested for all medicinal products for use in humans, irrespective of their eligibility for the centralised marketing authorisation procedure<sup>12,20</sup>. While SA is issued by the Committee for Medicinal Products for Human Use (CHMP), it is based on the recommendation of the Scientific Advice Working Party (SAWP), a multidisciplinary expert group that comprises a chairperson and up to 36 members selected based on complimentary scientific expertise. Its combined expertise covers a broad range of therapeutic areas, as well as multiple aspects of the drug development process including manufacturing, preclinical pharmacology and toxicology, clinical pharmacology and pharmacokinetics, gene and cell therapies, clinical trials, and statistics. Furthermore, the SAWP has access to a network of European experts and regularly interacts with the FDA, Health Technology Assessment Bodies (HTABs), the WHO, and patient organisations. The SAWP provides SA based on the applicant's position on the questions asked and on current scientific knowledge, which will be sent as a SA

letter to the applicant following adoption by the CHMP. While SA is not legally binding for either the applicant or the EMA, it is taken into consideration during the review of the marketing authorisation application (MAA), and any deviations from the provided SA needs to be well justified by the applicant. Although applicable throughout the EU, CHMP SA usually does not preclude additional consultations with national competent authorities (NCAs).<sup>12,13</sup> Importantly, SA is intended to support an efficient MAA evaluation by providing guidance on the requirements and generation of appropriate data for benefit-risk assessment, it is not a pre-evaluation of data to support a planned MAA or evaluate approvability of the product.<sup>1,14</sup>

#### **Benefits for developers of medicines**

The SA procedure is particularly of interest for developers of innovative medicines for rare indications and for products where guidelines are insufficient, or when a developer plans to deviate from the scientific guidelines in their develop-

ment plan. Furthermore, requesting SA is particularly recommended for small and medium enterprises (SMEs) and start-ups, as it gives access to high-level scientific scrutiny at reduced fees. SA promotes a more efficient use of resources during product development by providing feedback on the most suitable study designs and methodologies and reducing the risk of deficiencies in study designs at later stages. Compliance with the obtained SA has a major impact on the probability of a successful MAA outcome. Between 2000 and 2012, the MAA success rate for applicants whose trial design was considered as acceptable at the time of SA, or who modified a trial design to follow the SA recommendation, was 85% compared to 41% of those who had non-compliant trial designs.<sup>15</sup> Furthermore, SA-compliant trial design was also associated with fewer major objections during CHMP review.<sup>15</sup> These benefits for companies are reflected by the continuous strong uptake of the voluntary SA procedure, with 549 SA procedures in 2019, representing a 18% increase from 2018.<sup>11</sup>

## **EMA scientific advice procedure**

### **Process and timelines**

The initial phase of the SA procedure (Table 1 and Figure 2) requires the submission of a letter of intent (LoI) and/or a draft briefing document to the EMA Secretariat three weeks before the intended start of the procedure, or approximately seven weeks if a pre-submission meeting is requested.<sup>12</sup> Upon forwarding to the SAWP, two coordinators are appointed to manage the SA procedure. As the SAWP meets monthly 11 times per year (no meeting in August), missing a relevant submission deadline delays the procedure at least one month. Although referred to as "draft" in the EMA guidelines, the submitted briefing document must be considered as final by the applicant; however, further changes may be required by the EMA. This initial phase is completed with the validation of the briefing document by the SAWP and the submission of the final briefing package via Eudralink by the applicant. The actual SA procedure (Figure 2) begins with a review of the briefing package by the SAWP coordinators and the preparation of a first report. The SAWP will discuss this report and decide whether the SA can be adopted without meeting the applicant (40 days procedure) or whether the applicant will be invited to

a discussion meeting (70 days procedure). In the latter case, the list of issues raised by the SAWP is addressed during a 90-minute meeting, which takes place at around day 60 and is usually held face-to-face (F2F). Subsequently, the SAWP coordinators will then send their joint report to the Agency Secretariat though currently due to the COVID-19 pandemic all meetings are held virtually until at least the end of 2020. Following peer review by the SAWP, CHMP, and the EMA, the final advice letter is adopted by the CHMP and sent to the applicant. Of note, while confidential in the pre-authorisation phase, SA will be included in the European public assessment report at the time of marketing authorisation after redaction of confidential information.<sup>13-14</sup> Depending on the scope, the fee for SA currently ranges from 44,400€ to 89,000€, although reductions up to 100% can be granted for certain types of submissions, e.g., if

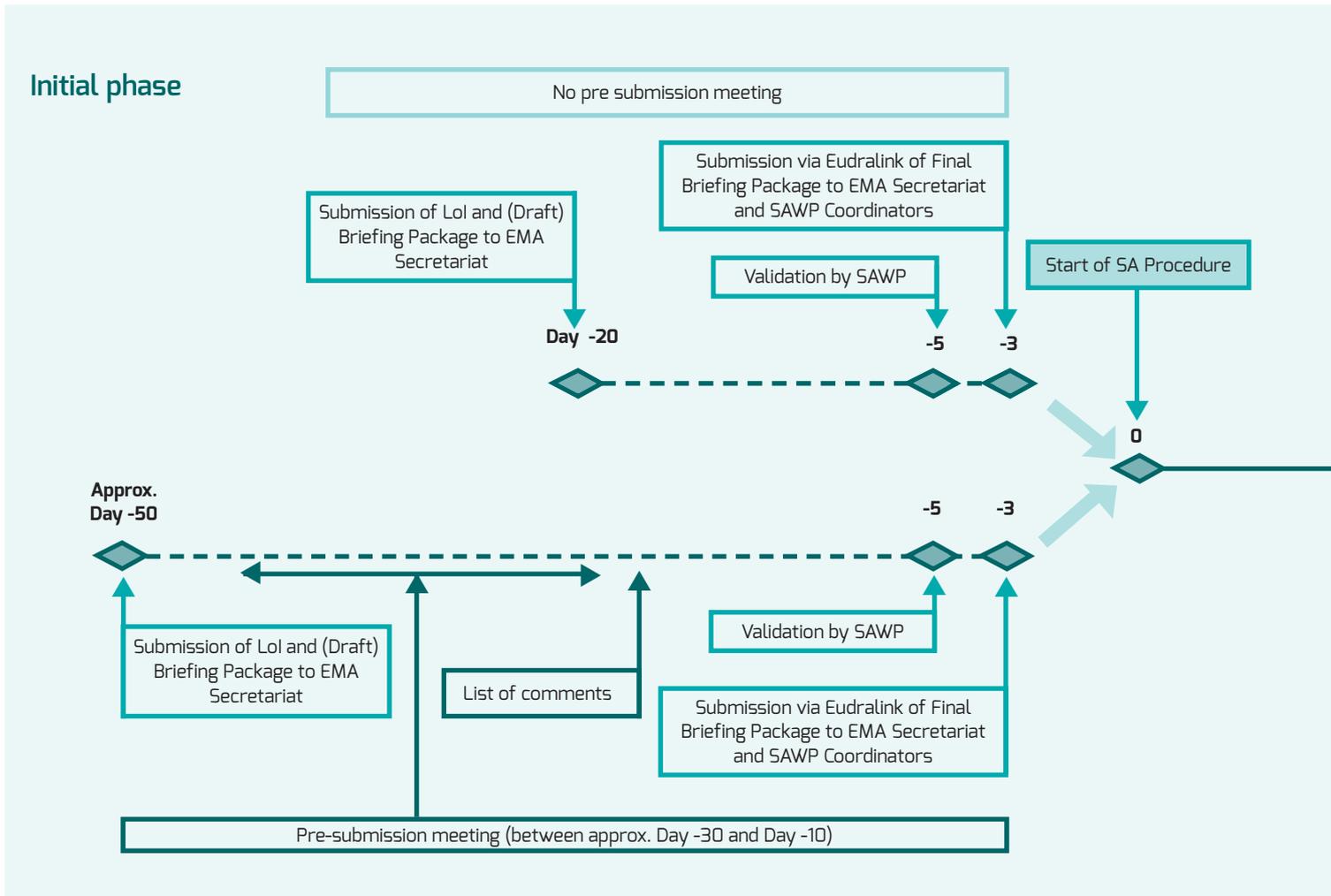
applicant is a SME and/or the developer holds an orphan drug designation (ODD) for the concerned product.<sup>13,16</sup>

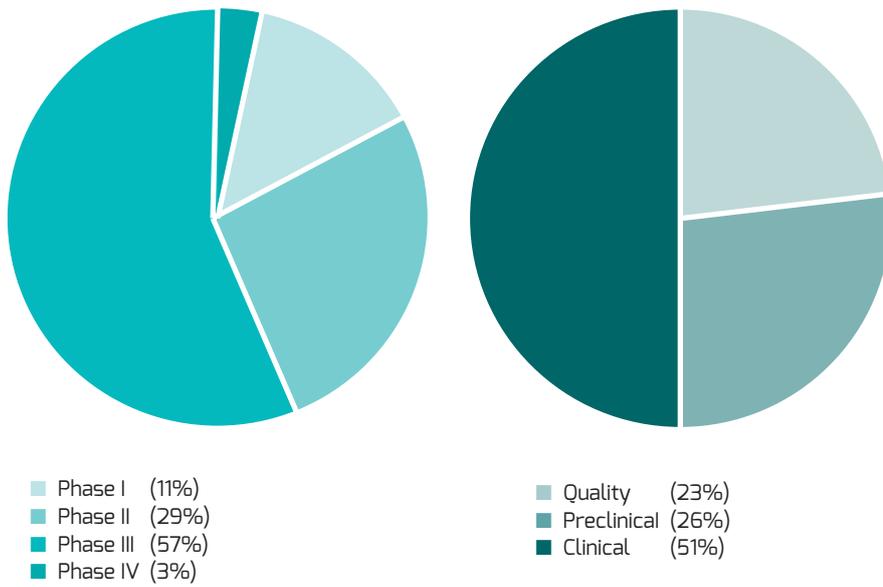
**Scope of questions**

SA can be requested at any point of product development, including the post-marketing phase. Questions can relate to any part of the development process, including quality, non-clinical, and clinical aspects as well as methodological issues such as statistical tests, data analysis, and modelling and simulation. Further topics in scope of SA include biosimilar development, risk-management plans, paediatric and geriatric development, or orphan drug development (see “protocol assistance for orphan medicines” below). In 2019, the majority of SA requests were related to medicines in phase III of clinical development and to clinical aspects (Figure 3).<sup>10</sup>

**Document requirements**

For both LoI and the briefing document, the use of the templates available on the EMA website is highly encouraged. The briefing document is the core of the SA request and consists of three main parts: I. summary, II. question(s) and applicant’s position(s), and III background information on the product. The summary (part I), which should typically not be longer than three pages, contains background information on the disease to be treated and a brief description of the product including quality, non-clinical and clinical development, its regulatory status, and an explanation of the rationale for seeking SA. The questions (part II) are grouped according to the area of expertise and numbered sequentially. Questions should be phrased carefully, clearly, and unambiguously to obtain a clear and precise answer, and their scope neither too broad nor too narrow to obtain meaningful advice. Typically,





questions are phrased starting with “Does the CHMP agree that/with” followed by the applicant’s proposal, which is detailed and justified in the applicant’s position following each question. The applicant’s position includes a comprehensive justification of the chosen approach, including the context and consideration of alternative options, with a critical discussion of the relative advantages and disadvantages of each approach. With a recommended length of 1–3 pages, each applicant’s position should contain sufficient detail to serve as a “stand-alone” argument, supported by cross-references to relevant parts of the briefing document or annexes supporting the argument, as needed. The background information (part III) provides a comprehensive overview of the medicine’s development programme and presents detailed information on quality, non-clinical, and clinical aspects; though consideration should be

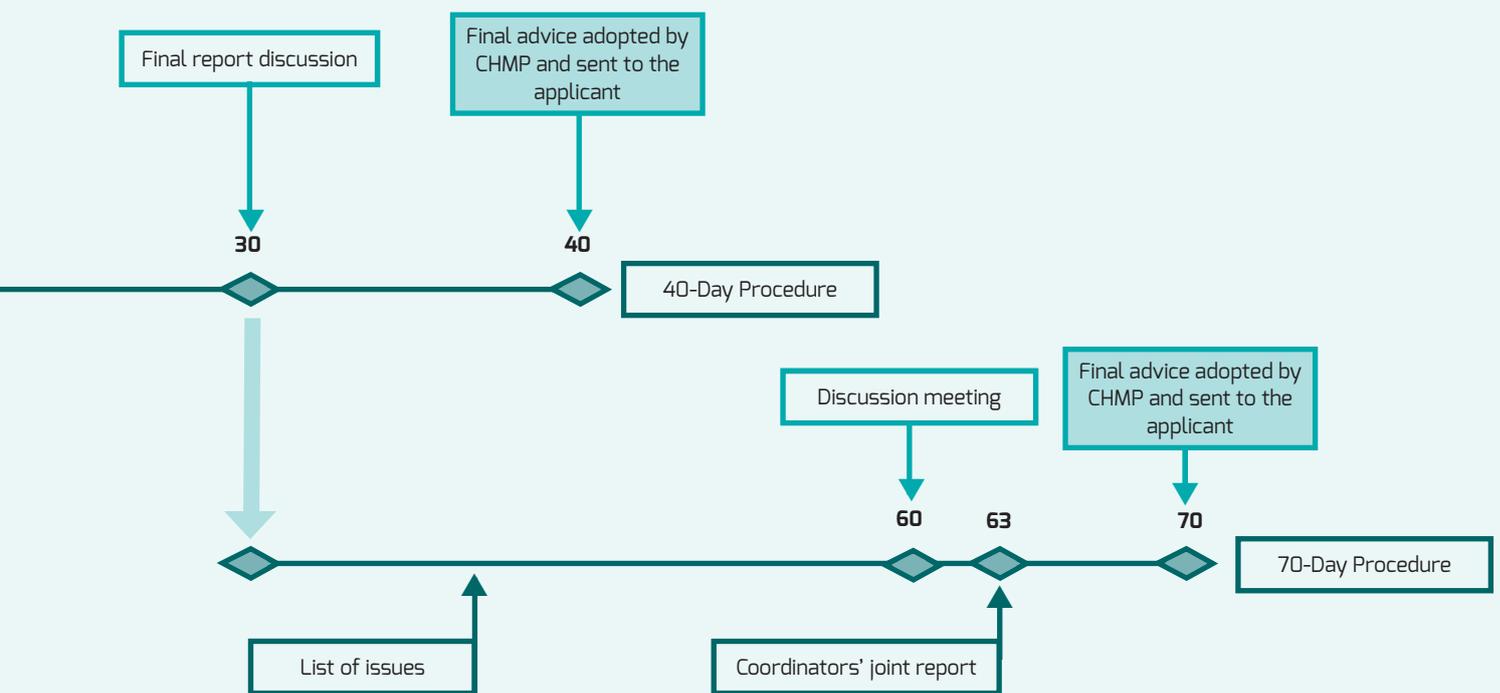
Figure 3. Scope of scientific advice and protocol assistance requests in 2019

Source: EMA annual report 2019.<sup>11</sup>

## SA procedure

Figure 2. European Medicines Agency scientific advice procedure timeline

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; LoI, letter of intent; SA, scientific advice; SAWP, scientific advice working party  
Image prepared by SFL Regulatory Affairs & Scientific Communication GmbH.





given to the content and level of detail to keep the overall size of the briefing document reasonable. Tabulated summaries are in the background section and are particularly helpful to keep information comprehensive yet concise. Finally, the final briefing package typically includes relevant annexes, such as the investigator's brochure, clinical study protocols, reports or synopses, previously received SA by the EMA or other regulatory agencies, regulatory documents such as ODDs or agreed paediatric investigation plans and literature references.<sup>12</sup> If the SA procedure includes a discussion meeting, this requires the applicant to prepare a response to issues to be addressed in writing prior to the discussion meeting and slides for a presentation and discussion of issues during the F2F meeting.

## Special EMA scientific advice procedures

### Protocol assistance for orphan medicines

Protocol assistance (PA) specifically refers to SA for orphan medicines. PA can be requested prior to MAA submission by applicants who have received ODD for the concerned product and follows the same procedure as regular SA (Table 1).<sup>13</sup> Beyond the typical scope of SA, PA can also include topics specifically relevant for the development of orphan drugs, i.e., the clinical

development strategy to generate the appropriate data for demonstration of significant benefit within the designated orphan indication or in relation to orphan similarity.<sup>4,13</sup> Between 2000 and 2013, 55% of applicants of orphan MAAs requested advice, compared to 42% for non-orphan MAAs. Similar to SA, the number of PA requests increased over the years (Figure 1) and compliance with PA was associated with a higher MAA success rate, compared to non-compliance (80% vs 36%).<sup>21</sup>

### Parallel EMA-FDA scientific advice

The parallel scientific advice (PSA) programme has been established by the EMA and FDA in 2004 with the goal to encourage the dialogue between the agencies (Table 1), though its adoption so far has been limited by significant administrative and logistical resource requirements from the applicants. The PSA may be especially relevant for applicants developing important medicinal products for which no development guidelines exist, or for which existing guidelines differ significantly between the agencies, or for products with significant clinical safety, animal toxicology, or unique manufacturing challenges. Through PSA, the agencies will have the opportunity to discuss the applicant's question with each other and will try

to provide convergent responses; however, each advice is independent and may differ between the agencies. Furthermore, each agency will retain its individual regulatory decision-making authority regarding drug development issues and marketing applications.<sup>17,18,22</sup>

### Parallel consultation with EMA and Health Technology Assessment Bodies

Since July 2017, EMA and the European Network for Health technology Assessment (EUnetHTA) offer a parallel consultation procedure to assist in the generation of the necessary evidence to simultaneously support both the MAA of new medicines and their reimbursement (Table 1). This parallel procedure provides opportunities for mutual discussion, understanding, and problem solving between EMA and HTABs. Additionally, this new procedure facilitates the centralised recruitment of HTABs through the EUnetHTA, avoiding the requirement to contact each HTAB individually.<sup>19,23</sup>

### Qualification of novel methodologies

A dedicated SA procedure called qualification process supports the development of novel methodologies in medicine development (e.g., the use of a novel biomarker or clinical endpoint), resulting in either a CHMP quali-

Table 1. Overview of general and special EMA scientific advice procedures

SA procedure	Duration of the procedure and milestones	Documents required
EMA SA <sup>13</sup>	<p>Overall duration: 60 to 115 days</p> <ul style="list-style-type: none"> <li>● Day -45 or -20: LoI and draft briefing document submission</li> <li>● Day -3: Final briefing package submission</li> <li>● Day 0: Procedure starts</li> <li>● Day 40: EMA sends response (if no issues were found by the SAWP that required clarification)</li> <li>● Day 70: EMA sends response (if SAWP had further issue to be addressed in writing and/or at a discussion meeting)</li> </ul> <p>See Figure 2 for detailed timeline</p>	<ul style="list-style-type: none"> <li>● LoI</li> <li>● Briefing package including: <ul style="list-style-type: none"> <li>● Part I: summary</li> <li>● Part II: list of question and applicant's position</li> <li>● Part III: background information</li> <li>● Annexes and References</li> </ul> </li> </ul>
Protocol Assistance <sup>13</sup>	<ul style="list-style-type: none"> <li>● Same as for general EMA SA procedure</li> </ul>	<ul style="list-style-type: none"> <li>● Same as for general EMA SA procedure</li> </ul>
Parallel EMA-FDA <sup>17, 18</sup>	<p>Overall duration: 110 to 135 days</p> <ul style="list-style-type: none"> <li>● Day -45 to -20: LoI and draft meeting package submission + EMA/FDA agreement to PSA request</li> <li>● Day -5: Final meeting package submission</li> <li>● Day 0: Procedure starts</li> <li>● Day 30: EMA-FDA meeting (integrated into the regular SAWP meeting schedule)</li> <li>● Day 60: EMA-FDA-applicant meeting</li> <li>● Day 70: EMA sends response</li> <li>● Day 90: FDA sends response</li> </ul>	<ul style="list-style-type: none"> <li>● PSA request to both agencies</li> <li>● EMA only: <ul style="list-style-type: none"> <li>● LoI</li> <li>● Briefing package as for EMA SA/PA</li> </ul> </li> <li>● FDA only: <ul style="list-style-type: none"> <li>● Meeting package</li> </ul> </li> </ul>
Parallel EMA-HTABs <sup>19</sup>	<p>Overall duration: 150 days</p> <ul style="list-style-type: none"> <li>● Day -60: LoI submission (with draft briefing package if requesting pre-submission meeting via TC)</li> <li>● Day -30: Draft briefing package submission (or pre-submission meeting via TC)</li> <li>● Day -15: Written comments on the draft briefing document sent to the applicant</li> <li>● Day -2: Revised meeting package submission</li> <li>● Day 0: Procedure starts</li> <li>● Day 32: List of issues sent to the applicant</li> <li>● Day 45: Written responses submission</li> <li>● Day 56: Presentation and list of participants submission</li> <li>● Day 60: EMA-HTABs-applicant F2F meeting</li> <li>● Day 70: EMA sends response upon CHMP adoption</li> <li>● Day 90: EUnetHTA sends response</li> </ul>	<ul style="list-style-type: none"> <li>● LoI</li> <li>● Briefing package following the EMA-EUnetHTA common briefing document template</li> </ul>
Qualification of novel methodologies <sup>20</sup>	<p>Overall duration: 160 (qualification advice) or 250 days (qualification opinion)</p> <ul style="list-style-type: none"> <li>● Day -60: LoI and draft briefing document submission</li> <li>● Day -15: EMA-applicant preparatory meeting (F2F or TC)</li> <li>● Day -3: Final briefing package submission</li> <li>● Day 0: procedure starts</li> <li>● Day 30: List of questions sent to the applicant</li> <li>● Day 60: Discussion with the applicant (additional interactions are possible via TC)</li> <li>● Qualification advice: <ul style="list-style-type: none"> <li>● Day 100: Response sent to the applicant</li> </ul> </li> <li>● Qualification opinion: <ul style="list-style-type: none"> <li>● Day 130-190: Public consultation</li> <li>● Day 190: Response sent to the applicant</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● LoI</li> <li>● Briefing package</li> <li>● Qualification advice: <ul style="list-style-type: none"> <li>● Draft protocols</li> <li>● Development plans for future studies and supportive data</li> </ul> </li> <li>● Qualification opinion: <ul style="list-style-type: none"> <li>● Protocols</li> <li>● Study reports and supportive data</li> </ul> </li> </ul>

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EUnetHTA, European Network for Health Technology Assessment; F2F, face-to-face; LoI, letter of intent; PA, protocol assistance; HTAB, Health Technology Assessment Bodies; PSA, parallel scientific advice; SA, scientific advice; SAWP, scientific advice working party; TC, teleconference



fication advice or opinion (Table 1). For a qualification advice, the CHMP evaluates the scientific rationale and the submitted preliminary data and issues an advice on protocols and procedures for further development of a method towards qualification. For a qualification opinion, the CHMP evaluates the submitted data and issues a decision on the acceptability of the use of a new method in medicine development. As the scientific knowledge of a new method can evolve over time, the qualification process may involve an ongoing interaction between the applicant and EMA. Additionally, the information is shared with the scientific community prior to the adoption of the qualification opinion to promote scrutiny and discussion. After the qualification process, the EMA may also amend the relevant guidance to implement the newly qualified methodology.<sup>1,20</sup>

### National scientific advice procedures

SA can also be requested from NCAs of EU member states. Although the general purpose of national SA is in line with the EMA SA procedure, some differences may exist in terms of document requirements and timelines (Table 2.)<sup>24-31</sup> Compared to the EMA SA procedure, obtaining SA from an NCA is usually faster and

it may offer more opportunities for discussion meetings to also cover virtual meetings due to COVID-19 (Table 2).

### Pilot simultaneous national scientific advice procedure

The simultaneous national scientific advice procedure (SNSA) was introduced to optimise resources and improve regulatory support when an applicant requests SA from different NCAs. The SNSA pilot started on February 1, 2020, and currently allows simultaneous contact with two NCAs. Following an evaluation at the end of 2020 based on the experience from the perspective of the NCAs and the applicants with the SNSA pilot, an optimised best practice approach which will include more than two NCAs will be developed.<sup>32,33</sup>

### Rapid scientific advice for COVID-19 treatments and vaccines

Similar to the response to past public health threats like Ebola,<sup>34</sup> the EMA has set up accelerated procedures to speed up development

and approval of medicines and vaccines for the treatment and prevention of COVID-19. These procedures include a rapid SA procedure, which is available for initial MAA of new active substances and indication extension applications for authorised medicines repurposed for the treatment of COVID-19. This rapid SA procedure is free of charge, there are no specific submission deadlines, and its timeline is reduced

to only 20 days from the original 40–70 days, with more flexibility on the type and extent of briefing package based on a case-by-case agreement.<sup>35</sup>

### Role of the medical writer in the scientific advice procedure

Because clear communication is key for applicants to obtain appropriate and useful SA, medical writers play an important role in the preparation of the briefing document, in collaboration with regulatory affairs

and relevant subject matter experts who provide input to the questions and applicant's positions. Importantly, medical writers can support the phrasing of clear, concise questions and drafting

Furthermore, the EMA is constantly updating existing processes and launching new pilot projects to further expand the available options.

Table 2. Overview of document requirements for selected national scientific advice procedures

Country/agency	Timeline for submission of documents	Documents required
<b>Denmark</b> Danish Medicines Agency – Lægemiddelstyrelsen <sup>24</sup>	<ul style="list-style-type: none"> <li>Initial documents at least 2-3 months before the proposed meeting date               <ul style="list-style-type: none"> <li>Application form</li> <li>List of questions</li> <li>Background to questions (where possible)</li> </ul> </li> <li>Final presentation and/or briefing document at least 2-3 weeks before meeting date</li> </ul>	<ul style="list-style-type: none"> <li>Application form (Lægemiddelstyrelsen website)</li> <li>List of questions</li> <li>Background to questions (max. 30 pages)</li> <li>Final presentation and/or briefing document</li> </ul>
<b>France</b> National Agency for the Safety of Medicine and Health Products – ANSM <sup>25</sup>	<ul style="list-style-type: none"> <li>Meeting request usually 2 months prior to proposed meeting date</li> <li>Briefing document at least 3 weeks before the meeting</li> </ul>	<ul style="list-style-type: none"> <li>Cover letter</li> <li>Briefing document including background information, list of questions with applicant's position and investigator's brochure</li> </ul>
<b>Germany</b> BfArM – Federal Institute for Drugs and Medical Devices <sup>26</sup>	<ul style="list-style-type: none"> <li>Standard procedure:               <ul style="list-style-type: none"> <li>Full package at time of initial application</li> </ul> </li> <li>Procedure with supplemental submission:               <ul style="list-style-type: none"> <li>List of questions without documentation at time of initial application</li> <li>Documentation at least 4 weeks prior to meeting date</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Cover letter (signed pdf)</li> <li>Application form (BfArM website, signed pdf)</li> <li>List of questions (BfArM website “Appendix Questions”, word or pdf format)</li> <li>Briefing document (max. 50 pages, pdf format)</li> <li>List of meeting participants (BfArM website “Appendix Participants”, word or pdf)</li> </ul>
<b>Germany</b> Paul-Ehrlich-Institute – Federal Institute for Vaccines and Biomedicines <sup>27</sup>	<ul style="list-style-type: none"> <li>Request form 8-12 weeks prior to proposed meeting date</li> <li>Briefing document at least 3 weeks prior to meeting date</li> </ul>	<ul style="list-style-type: none"> <li>Request form (PEI website)</li> <li>Briefing document (max. 40 pages)</li> </ul>
<b>Netherlands</b> MEB – Medicines Evaluation Board <sup>28</sup>	<ul style="list-style-type: none"> <li>Meeting request (application form with draft list of questions) (usually 1.5-3 months ahead of the planned meeting date)</li> <li>Documentation, presentation, and list of attendees at least 3 weeks prior to meeting date</li> </ul>	<ul style="list-style-type: none"> <li>Application form (MEB website)</li> <li>Briefing document</li> <li>List of participants</li> </ul>
<b>Spain</b> AEMPS – Spanish Agency for Medicines and Health Products <sup>29</sup>	<ul style="list-style-type: none"> <li>Meeting request (application form, usually 2-3 months ahead of the planned meeting date)</li> <li>After validation of the request, documents should be sent at least 30 days before the meeting</li> </ul>	<ul style="list-style-type: none"> <li>Application form (AEMPS website)</li> <li>LoI</li> <li>List of questions and applicant's position</li> <li>Other relevant documents: Previous SA or reports, guidelines, references</li> </ul>
<b>Sweden</b> Läkemedelsverket – Swedish Medical Products Agency <sup>30</sup>	<ul style="list-style-type: none"> <li>Application form with well-specified questions (usually 2-3 months ahead of the planned meeting date)</li> <li>Full documentation at least 3 weeks prior to meeting date</li> </ul>	<ul style="list-style-type: none"> <li>Application form (Läkemedelsverket website)</li> <li>Briefing document (max. 100 pages)</li> <li>List of questions (word format)</li> <li>List of meeting participants (word format)</li> <li>Other relevant documents, e.g. references, investigator's brochure</li> </ul>
<b>United Kingdom</b> Medicines and Healthcare products Regulatory Agency – MHRA <sup>31</sup>	<ul style="list-style-type: none"> <li>Meeting request (application form with draft list of questions) (usually 2-3 months ahead of the planned meeting date)</li> <li>Final briefing documents at least 10 days prior to meeting date</li> </ul>	<ul style="list-style-type: none"> <li>Request for scientific advice form (MRHA website)</li> <li>Briefing document:               <ul style="list-style-type: none"> <li>Final list of questions and applicant's position</li> <li>Presentation to be given at the meeting (if applicable)</li> </ul> </li> <li>Relevant appendices, e.g. background information, previous SA, guidelines</li> </ul>

Abbreviations: F2F, face-to-face; LoI, letter of intent; SA, scientific advice; TC, teleconference.

**Disclaimer:** Regulatory procedures and requirements are subject to change and it is strongly advised to consult the relevant agency's website for current information.



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# EU software regulations: The new normal or innovation stagnation?

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## Abstract

Advances in software and its application in a medical device and as a medical device have opened the door for many new technological capabilities in healthcare. Around the globe, government agencies have begun to take a heightened interest in how these devices are regulated. Whether it is software embedded in a medical device, software as a medical device, mobile medical applications, or artificial intelligence/machine learning mechanisms, there are potential risks to both user and patient. Cybersecurity is the gateway for evaluating vulnerabilities and protecting devices and patients. In this article, we examine how the EU has introduced new regulations regarding software, cybersecurity, and the impact on the total product life cycle development and innovation of new technologies. Privacy rules in compliance with the EU General Data Protection Regulation may present innovators with challenges by limiting AI's usage of patient data.

## Introduction

With the boom of the internet, the ubiquity of the smartphone, and exponential advancements in software technology and applications, it is no surprise that these developments have implications for the medical device industry and regulation. Across the world, regulators are reshaping the process of bringing medical devices to market either on a country-by-country basis or through collective initiatives. In recent years, we have seen the formation of the Global Harmonization Task Force, only to see it dissolve

based on individual interests of countries. We have also seen the formation of the International Medical Device Regulators Forum (IMDRF) whose mission it is to provide a global harmonised message regarding the regulation of medical devices.<sup>1</sup>

Among regulatory bodies, the FDA, it would appear, has had the most rigorous approach to regulating medical devices, as well as to staying ahead of the curve with technological advances. Most recently, there has been a surge in activity from other regulatory bodies including those in the EU, Australia, Canada, and Japan, to name a few, as they are now implementing stricter protocols for how medical devices are regulated and the requirements that must be met to bring them to market. The EU, for example, totally revamped its regulatory process with the implementation of the EU Medical Device Regulation of 2017 (EU MDR 2017/745).<sup>2</sup> The many changes include increased requirements of the clinical evaluation report, Notified Body accreditation, new General Safety and Performance Requirements (formally essential requirements checklist), and new regulations regarding software, and, in particular, “software as a medical device” (SaMD), not just “software in a medical device”.

For software in a medical device, regulations, standards, and guidance documents have been available for many years as the software in the devices has matured.<sup>3-7</sup> External to the medical device field, we have seen various types of malicious attacks on computer systems that either destroy or interrupt how these systems operate. The medical device industry has not been immune from cyber attacks. It was even determined that a stand-alone device – not connected to a computer network – can be subject to interference from unauthorised individuals. A new concept (depending on its usage), software as a medical device, has now become front and centre in the regulated medical device world. The EU along with the implementation of EU MDR 2017/745, has issued several guidelines on how stakeholders must address software concerns, whether it be in a medical device or as a medical device. Several industry standards serve to support these regulations. In this article, we will look at various

aspects of these regulations and consider the potential positive or negative effects on innovation.

## Software as a medical device

SaMD can best be described as software that utilises an algorithm (logic, set of rules, or model) that operates on data input (digitised content) to produce an output that is intended for medical purposes that are defined by the SaMD manufacturer. The risks and benefits posed by SaMD outputs are largely related to the risk of inaccurate or incorrect output of the SaMD, which may affect the clinical management of a patient.

Stand-alone software – SaMD – must meet the requirements of a medical device:

*‘Medical device’ means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) and does not achieve its primary intended action by pharmacological, immunological or metabolic.<sup>1</sup>*

As such, these SaMD “devices” must conform to the same requirements of other devices to be placed on the market in the EU under EU MDR 2017/745. The IMDRF also has a definition for SaMD,<sup>1</sup> which is included in IMDRF/SaMD WG/N10FINAL:2013. It is defined as “software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device”.

Examples of software as a medical device (SaMD) include the following:

1. IDx-DR, IDx LLC, a retinal diagnostic software device is a prescription software device that incorporates an adaptive algorithm to evaluate ophthalmic images for diagnostic screening to identify retinal diseases or conditions.
2. AccipioIx, by MaxQ-AI Ltd., is a software workflow tool designed to aid in prioritising the clinical assessment of adult non-contrast head CT cases with features suggestive of acute intracranial haemorrhage in the acute care environment. AccipioIx analyses cases

using an artificial intelligence algorithm to identify suspected findings. It makes case-level output available to a PACS/workstation for worklist prioritisation or triage.

3. QuantX is a computer-aided diagnosis (CADx) software device used to assist radiologists in the assessment and characterisation of breast abnormalities using MR image data.
4. ClearView cCAD, ClearView Diagnostics Inc., is a software application designed to assist skilled physicians in analyzing breast ultrasound images. ClearView cCAD automatically classifies shape and orientation characteristics of user-selected regions of interest (ROIs). The device uses multivariate pattern recognition methods to perform characterisation and classification of images.

The IMDRF in IMDRF/SaMD WG/N41FINAL:2017 – Software as a Medical Device Clinical Evaluation<sup>6</sup> outlines how developers and manufacturers should evaluate software from a clinical standpoint to establish the following:

- That there is a valid clinical association between the output of a SaMD and the targeted clinical condition (to include pathological process or state); and
- That the SaMD provides the expected technical and clinical data

A valid clinical association is an indicator of the level of clinical acceptance and how much meaning and confidence can be assigned to the clinical significance of the SaMD's output in the intended healthcare situation and the clinical condition/physiological state. Analytically and technically, analytical validation measures the ability of an SaMD to accurately, reliably, and precisely generate the intended technical output from the input data. Said differently, analytical validation:

- Confirms and provides objective evidence that the software was correctly constructed – namely, that it correctly and reliably processes input data and generates output data with the appropriate level of accuracy, and repeatability and reproducibility (i.e., precision); and

*Medical device means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) and does not achieve its primary intended action by pharmacological, immunological or metabolic.*

Across the world, regulators are reshaping the process of bringing medical devices to market either on a country-by-country basis or through collective initiatives.



Clinical validity is evaluated and determined by the manufacturer during the development of SaMD before it is distributed for use (pre-market) and after distribution while the SaMD is in use (post-market).

- Demonstrates that (a) the software meets its specifications and (b) the software specifications conform to user needs and intended uses.

The analytical validation is generally evaluated and determined by the manufacturer during the verification and validation phase of the software development lifecycle using a quality management system (QMS).<sup>8</sup>

Clinical validation is the third requirement of an SaMD. Clinical validation measures the ability of an SaMD to yield a clinically meaningful output associated with the target use of SaMD output in the target healthcare situation or condition identified in the SaMD definition statement.<sup>6</sup>

“Clinically meaningful” refers to the positive impact of an SaMD on the health of an individual

or population, to be specified as meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to the function of the SaMD (e.g., diagnosis, treatment, prediction of risk, prediction of treatment response), or a positive impact on individual or public health.

Clinical validity is evaluated and determined by the manufacturer during the development of SaMD before it is distributed for use (pre-market) and after distribution while the SaMD is in use (post-market). Clinical validation of SaMD can also be viewed as the relationship between the verification and validation results of the SaMD algorithm and the clinical conditions of interest. Clinical validation is a necessary component of clinical evaluation for all SaMD and can be demonstrated by either:<sup>6</sup>

- Referencing existing data from studies conducted for the same intended use;

- Referencing existing data from studies for a different intended use, where extrapolation of such data can be justified; or
- Generating new clinical data for a specific intended use.

The SaMD definition statement, as defined in *SaMD N12*,<sup>8</sup> is used by the SaMD manufacturer to identify the intended medical purpose of the SaMD (treat, diagnose, drive clinical management, inform clinical management), to state the healthcare situation or condition that the SaMD is intended for (critical, serious, non-serious), and to describe the core functionality of the SaMD. The rigour to meet these requirements is outlined in *IMDRF/SaMD G/N12FINAL:2014* and is based on the state of the healthcare situation or condition and the significance of information to be provided by the SaMD to the healthcare decision.<sup>8,9</sup>



## Artificial intelligence/ machine learning

**Artificial intelligence (AI)** is the mechanism through which human intelligence is incorporated into machines through a set of rules (algorithm). The term AI refers to something made by humans – a non-natural thing that has the ability to understand or think accordingly. It can also be interpreted as the capability to train a computer to act like the human brain in the way it thinks. AI focuses on three major aspects (skills): learning, reasoning, and self-correction.

**Machine learning (ML)** is the methodology of the way a computer learns automatically on its own through experiences it had and improves without being explicitly programmed. ML is an application or subset of AI. ML focuses on the

development of programs so that it can access data to use it for itself. The entire process makes observations of data to identify the possible patterns being formed and make better future decisions. The goal of ML is to allow the systems to learn by themselves through the experience, without any kind of human intervention or assistance. Additionally, *deep learning* is a subset of ML that utilises neural networks to mimic brain-like behaviour. DL utilises larger sets of data than ML and focuses on information processing patterns.<sup>10</sup>

AI and ML systems in medicine have the potential to significantly improve healthcare, for example, by offering earlier diagnoses of diseases or recommending optimally individualised treatment plans. Yet the emergence of AI/ML in medicine also creates challenges that regulators must pay attention to. Which medical AI/ML-based products should be reviewed by regulators? What evidence should be required to permit marketing for AI/ML-based software as a medical device (SaMD)? How can we ensure the safety and effectiveness of AI/ML-based SaMD that may change over time as they are applied to new data?<sup>10</sup>

## Mobile medical apps

Mobile apps that meet the definition of a medical device must comply with the requirements of EU MDR 2017/745. Many mobile apps are not medical devices, meaning they do not meet the requirement of medical device as defined in the EU.<sup>2</sup> The use of mobile technologies is opening up new and innovative ways to improve health and healthcare delivery. Mobile applications (apps) can help people manage their own health and wellness, promote healthy living, and gain access to useful information when and where they need it. Users include healthcare professionals, consumers, and patients.

The development of mobile medical apps can improve healthcare and provide consumers and health care professionals with valuable health information. As mobile platforms become more user friendly, computationally powerful, and readily available, innovators have begun to develop mobile apps of increasing complexity to leverage the portability that mobile platforms can

offer. Some of these new mobile apps are specifically targeted to assist individuals in their own health and wellness management. Other mobile apps are targeted to healthcare providers as tools to improve and facilitate the delivery of patient care.<sup>11,12</sup>

Device regulations focus only on the apps that present a greater risk to patients if they don't work as intended and on apps that cause smartphones or other mobile platforms to impact the functionality or performance of traditional medical devices. Similar to traditional medical devices, certain mobile medical apps can pose potential risks to public health. Some mobile medical apps may pose risks that are unique to the characteristics of the platform on which the mobile medical app is run.<sup>11,12</sup> An example is the interpretation of radiological images on a mobile device could be adversely affected by the smaller screen size, lower contrast ratio, and any uncontrolled ambient light of the mobile platform.

## General Data Privacy Regulation

Data are key aspects of AI/ML. Machine-learning algorithms require vast amounts of high-quality training data. However, organisations face a number of barriers limiting their ability to access the data necessary to take advantage of AI effectively.<sup>13</sup> In May 2018, the EU introduced the General Data Privacy Regulation (GDPR), the new European privacy law.<sup>14</sup> The GDPR creates specific rules for how individuals may access, rectify, transfer, and delete personal data held by third parties. All organisations doing business in the EU must comply

with the GDPR, although many have failed to do so.<sup>15</sup> Given AI's heavy reliance on data, the GDPR's rules for data have substantial implications for the development and use of AI, especially applications involving machine learning.<sup>16</sup>

GDPR has created an artificial scarcity of data by making it more difficult for organisations to collect and share data. In addition, it has made it more difficult for companies to use AI applications that automate decision-making regarding individuals using personal information.<sup>14</sup> As a

Machine-learning algorithms require vast amounts of high-quality training data. However, organisations face a number of barriers limiting their ability to access the data necessary to take advantage of AI effectively.

result, the GDPR has put the EU at a competitive disadvantage in the development and use of AI.

The GDPR generally prohibits organisations from using data for any purposes other than those for which they first collected it. Article 5 requires data be “collected for specified, explicit and legitimate purposes” and that the collected data be “adequate, relevant and limited to what is necessary”.<sup>17</sup> These two restrictions – purpose specification and data minimisation – significantly limit organisations’ innovation with data by restricting them from both collecting new data before they understand its potential value and reusing existing data for novel purposes. By imposing restrictions on the collection and use of data, the GDPR puts firms in the EU at a competitive disadvantage compared with firms in countries such as China, where companies have access to data on hundreds of millions of internet and mobile phone users.

The GDPR limits how organisations use personal data to make automated decisions about individuals in two ways. Article 22 of the GDPR establishes a right for individuals “not to be subject to a decision based solely on automated processing, including profiling, which produces legal effects concerning him or her, or similarly significantly affects him or her”.<sup>14</sup> This means whenever companies use AI to make a decision about individuals, the data subject has the right to have a human review that decision. This requirement makes it difficult and impractical for companies to use AI to automate many processes because they must develop a process for individuals who opt out of the automated one.<sup>4</sup>

Second, Articles 13–15 require organisations to provide individuals with “meaningful information about the logic involved” in automated decisions. This means firms must be able to explain how an AI system makes decisions that have a significant impact on individuals.<sup>17</sup> While the EU’s guidelines have clarified that these requirements do not necessarily require a full disclosure of the algorithm, the information provided should be “sufficiently comprehensive for the data subject to understand the reasons for the decision”.<sup>18</sup> This means organisations cannot always comply

with requirements to explain the logic involved in an algorithmic decision-making process.<sup>19</sup> And even when companies *can* potentially offer an explanation of the logic involved, they may not be able to do so in a way that is concise and uses plain language, as required by the GDPR. As a result, these regulations will force many businesses to not use certain types of AI systems, especially more sophisticated ones, even when they may be more accurate, safer, and more efficient than the alternatives. Therefore, unless amended, the GDPR is expected to have a negative impact on the development and use of AI in Europe, putting European firms at risk of a competitive disadvantage in the emerging global algorithmic economy.<sup>20</sup>

## Cybersecurity

Medical devices will always be subject to vulnerabilities, which cannot be eliminated entirely. From a defensive perspective, manufacturers and developers must take a multi-tiered approach to minimise threats.<sup>7</sup> MDCG 2019-16 Guidance on Cybersecurity for medical devices outlines steps required by developers to reduce/minimise risk to medical devices. The IMDRF has established a companion document to augment the EU guidance.<sup>5</sup>

Cybersecurity vulnerabilities can render medical devices and hospital networks inoperable, disrupting the delivery of patient care across healthcare facilities. Such occurrences may result in the delay of diagnosis and/or treatment that may lead to patient harm. The need for effective cybersecurity to ensure medical-device functionality and safety has become more important with the increasing use of wireless, Internet- and network-connected devices, portable media, and the frequent electronic exchange of medical device-related health information. In addition, cybersecurity threats to the healthcare sector have become more frequent, more severe, and, in turn, more clinically important.

Cybersecurity guidance by both the IMDRF and EU<sup>5,21</sup> outline procedures to develop medical devices to minimise the threat of attack to these devices. They include strategies for pre-

market development including: security requirement, risk management, cybersecurity management plans, labelling, post-market considerations, vulnerability remediation, and incidence response.<sup>2</sup>

## Conclusions

Medical devices are increasingly connected to the internet, hospital networks, and other medical devices to provide features that improve healthcare and increase healthcare providers’ ability to treat patients. These features also increase the risk of potential cybersecurity threats. Medical devices, like other computer systems, can be vulnerable to security breaches, potentially affecting the safety and effectiveness of the device.

The European Union has implemented guidelines that address what developers and manufacturers of medical devices must do to address safety concerns. While these guidelines directly address concerns of cybersecurity and which types of software can be considered medical devices, these guidelines may impose an undue burden with regard to bringing devices to market in the EU. Restrictions on how personal data may be used for AI algorithm development and requirements for clinical validation, which may be lengthy and costly, could inhibit innovation.

Thus, the developer of software products intended for market in the EU must consider the cost of development against these new guidelines and regulations and determine the least burdensome approach to address them. Furthermore, they must take into consideration global regulations and how best to comply with the different requirements of other regulatory bodies. Therefore, developers may choose to first market new and innovative device first in regions with less-stringent requirements than the EU. Overall, the development of software devices may benefit from a global harmonised set of requirements.

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## Conflicts of interest

The author declares no conflict of interest.

Cybersecurity vulnerabilities can render medical devices and hospital networks inoperable, disrupting the delivery of patient care across healthcare facilities.

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# The new PubMed – underestimated regulatory obstacles?

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## Abstract

NCBI's PubMed is a powerful literature retrieval tool widely utilised in many areas including science and regulatory affairs. In regulatory affairs, PubMed searches are employed to identify clinical evidence pertinent to product approval processes. To ensure traceability and reproducibility, a highly structured literature search strategy is advised, as laid out in numerous guidance documents issued by regulatory agencies such as the European Commission and the International Medical Device Regulators Forum.

Recently, a new version of PubMed was deployed, including a new user interface and, less visibly, potential changes to search algorithms, which may affect the results delivered by search strings. To unravel potential differences among the legacy and new version of PubMed, head-to-head comparisons with increasing search complexity were performed.

For the new version of PubMed, the user

interface was redesigned and allows feature customisation. Importantly, as compared to the legacy version of PubMed, the new PubMed delivered diverging numbers of search hits. Of note, the PubMed inherent result sorting methods produced alternating search hit numbers only in the legacy version. Intriguingly, each version identified literature that was not found by the respective other version, although these publications were considered relevant in the search context. Technically, translation of entered search strings into detailed search strings varied between interfaces.

Differences between the legacy (online at least until September 30, 2020) and the new version were found, affecting the traceability, reproducibility, and reliability of PubMed data used for approval processes.

## Introduction

The National Institutes of Health (NIH) and its subsidiary organisation the National Center for Biotechnology Information (NCBI) provide access to biomedical and genomic information enabling scientific progress. One of the most popular resources developed and maintained by the NCBI is PubMed – the main entry point to the rich content of the Medline database. On an average working day, approximately 2.5 million users from around the world access PubMed to perform about 3 million searches and view 9 million pages.<sup>1</sup> PubMed is optimised for biomedical electronic research<sup>2</sup> and strategies on improving search techniques have been published.<sup>3</sup>

PubMed is a free resource supporting the search and retrieval of biomedical and life sciences literature from more than 30 million citations from MEDLINE, life science journals, and online books. PubMed citations and abstracts cover the fields of biomedicine and health, including portions of the life sciences,

behavioural sciences, chemical sciences, and bioengineering. The exponential increase in available scientific literature renders data extraction more and more difficult. To deal with the challenges of large and complex databases, tools are under development to identify and extract relevant literature.<sup>4</sup> Indeed, the NIH revised the PubMed interface to meet users' needs. To accommodate changing user needs, a number of new features have been added to PubMed in recent years, such as sorting of results by relevance, faceted search, query auto-suggest, and author name disambiguation.<sup>1</sup> On October 21, 2019, the NCBI issued a blog entry introducing a new version of PubMed.<sup>5</sup>

PubMed is commonly used in a broad array of biomedical disciplines such as academic basic research and, moreover, in the field of medical device regulatory affairs. The implementation of PubMed searches in regulatory affairs procedures, especially during medical device regulatory approval, was widely recognised, however, has been subject to debates in the last decades. Back in the early 2000s, the FDA exempted new medical devices from clinical trials if manufacturers could confirm similarity to another

product already on the market. The European Union established a similar conformity assessment procedure for new medical devices.<sup>6</sup> Therefore, a CE mark might be awarded in cases of "existing similarity", where the new device closely resembles existing technical, clinical, and biological features.<sup>7</sup> Thus, approval of new medical devices via the similarity route is a powerful approach to facilitate market access, often without having to carry out pre-market clinical investigations with a new product. However, market observations revealed that relying

on this approach occasionally resulted in faulty or ineffective medical devices that can harm the users' health and gain market access. Procedural failures possibly involving insufficiently structured literature searches (e.g., due to inappropriate search limitations, inadequate use

Supplementary tables and figures are available online for this article at:  
<https://pro-liance.com/the-new-pubmed/>



of Boolean operators or application of unsuitable search terms), but also constraints of the similarity principle's applicability, for instance, allowed metal-on-metal (MoM) hip implants to reach the market. MoM hip implants were often approved on the basis of similar products that were recalled or removed from the market later on. Kynaston-Pearson et al. revealed that a considerable number of hip replacement implants on the market lacked evidence for clinical efficacy, precluding safe clinical use.<sup>7</sup> Moreover, regulatory agencies informed about serious health concerns associated with MoM hip implants.<sup>8,9</sup>

Nowadays, more than ever, clinical evidence gained from clinical investigations testing the medical device of interest is considered the gold standard to support the safety and efficacy of a medical device. This is in line with the provisions laid down in ISO14155, an international standard that addresses good clinical practices for design, conduct, recording, and reporting of clinical investigations carried out in human subjects to assess safety and performance of medical devices for regulatory purposes.<sup>10</sup> To avoid the aforementioned difficulties after approval, the literature search for the similarity route must follow distinct

rules and deliver reliable searchability and accessibility of encompassing literature databases. The pertinent literature search must be clear, concise, systematic, traceable, and reproducible as laid out in the MEDical DEVICES Documents (MEDDEV) 2.7/1 rev.4<sup>11</sup> and in the International Medical Device Regulators Forum document (IMDRF) MDCE WG/ N56FINAL: 2019,<sup>12</sup> and the evaluation has to consider favourable as well as unfavourable results.

As service providers supporting the efforts of medical device manufacturers to ensure initial and continued market access, we are aware of the pitfalls associated with the literature search applied for the similarity route. Major concerns are always related to traceability and reproducibility. Changes to database functionality, including, but not limited to the journals covered, amendments to the user interface, and modifications in article indexing and search algorithms, can have a substantial effect on the quality and reproducibility of searches. After recognising that a new version of PubMed was deployed by the NCBI, we wondered whether the search results might differ and how traceability and reproducibility might be affected.

## Methods

The following web pages were compared side-by-side:

- 1 <https://pubmed.ncbi.nlm.nih.gov/> (new version of PubMed)
- 2 <https://www.ncbi.nlm.nih.gov/pubmed/> (legacy version of PubMed; nowadays the link immediately redirects to the new version of PubMed)
- 3 <https://pmlegacy.ncbi.nlm.nih.gov/> (current connection to the legacy version of PubMed), which is available at least until October 31, 2020.

To search PubMed, results were sorted by “most recent”, unless otherwise indicated in the main text.

To assess variations in database (DB) output, different search terms relating to distinct areas (immunology/immunological diseases and medical devices) were defined. Four different searches with increasing complexity were performed. The following search terms were used:

- 1 *ventilation and ARDS (Medical device search (MD) #1)* and
- 2 *(metal-on-metal hip implants) AND (compli-*

cations OR adverse events) AND surgery (MD #2)

- 3 IL-31 (Immunology search (Im) #1) and
- 4 (atopic dermatitis OR atopy) AND (skin OR dermis OR cutaneous OR dermal) AND (IL-31 OR IL-4) AND (antibody) (Im #2).

To add even more complexity, the searches were limited to certain time frames as indicated in the main body of text.

The differences regarding layout, handling, translation of search terms, traceability, and reproducibility were assessed.

Relevance of publications retrieved was mainly determined based on the title only. In individual cases, the abstract was checked to assess relevance in the search context. Importantly, in the common regulatory literature appraisal process, both title and abstract are considered for decision making. Here, for time reasons, the abstract was not factored in in most cases for the relevance determination.

Results of the searches Im #1 and #2 are presented in an online supplement to this article, available at <https://pro-liance.com/the-new-pubmed/>. Importantly, the early searches are employed to identify technical and visual updates associated with the new PubMed as compared to the legacy version of PubMed.

## Results

This short investigation was intended to identify differences between the legacy and the new PubMed user interfaces, operational procedures, search results, and the overall traceability and reproducibility of results. The results section is divided in two major areas: 1. medical devices, and 2. immunology/immunological diseases.

### Medical devices - Search for and translation of a 2-term search query (MD #1)

To evaluate the translation process for search queries with moderate complexity, a sample search was conducted using the terms *Ventilation* AND *ARDS*. Searches conducted with the legacy and the new version of PubMed delivered 4697

and 5116 hits, respectively (performed on November 19, 2019, sort by “most recent”). Of note, a later search using the same above-mentioned terms revealed 4714 and 4685 hits for the legacy and new version of PubMed, respectively (performed on December 5, 2019, sort by “most recent”). More iterations performed on January 16 and March 6, 2020, retrieved 4745 and 4801 results for the legacy version and 4715 and 5237

for the new version, respectively. Together, the number of hits increased constantly for the legacy search engine, as it would be expected since over time more publications are added to the database. However, the new PubMed delivered alternating numbers of search hits during the observational period (Figure. 1).

Sorting by “best match” yielded 5118 (legacy version) and 5116 hits (new version) (performed on November 19, 2019). Again, a later search showed different results. Here, 4687 and 4685 hits for the legacy and new version of PubMed, respectively, were found (performed on December 5, 2019). In contrast to the legacy version of PubMed, no difference in terms of hit numbers between “most recent” and “best match” was identified for the new version of PubMed (Table 1). Interestingly, the number of hits in “best match” mode decreased for the legacy and new version of PubMed.

The legacy version of PubMed translated the entered search string into:

(“ventilation” [MeSH Terms] OR “ventilation” [All Fields] OR “respiration” [MeSH Terms] OR “respiration” [All Fields]) AND

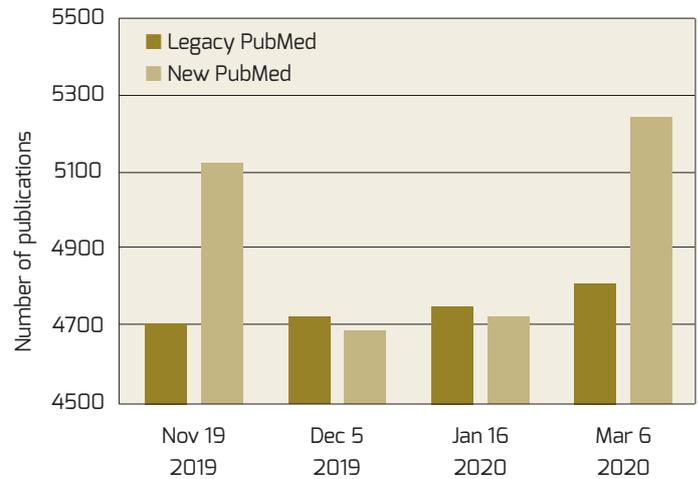


Figure 1. Development of number of search hits within the time frame from Nov 19, 2019, through March 6, 2020

ARDS [All Fields] (performed on December 5, 2019).

Instead, the query generated by the new version of PubMed showed a higher level of complexity in terms of search string translation:

(((((“ventilated” [All Fields] OR “ventilates” [All Fields]) OR “ventilating” [All Fields]) OR “ventilation” [MeSH Terms]) OR “ventilation” [All Fields]) OR “respiration” [MeSH Terms]) OR “respiration” [All Fields]) OR “ventilate” [All Fields] OR “ventilations” [All Fields]) OR “ventilator’s” [All Fields] OR “ventilators, mechanical” IAND “mechanical” [All Fields])) OR “mechanical ventilators” [All Fields] OR “ventilator” [All Fields] OR “ventilators” [All Fields] OR “ventillation” [All Fields] AND “ARDS” [All Fields], (performed on December 5, 2019).

### Medical devices – Search for and translation of a multi-term search query (MD #2)

A composite search was executed for a search string related to a recurrent topic in the medical device industry – MoM hip implants. Here,

Table 1: Comparative description of retrieved search results

Date of search	Legacy version of PubMed		New version of PubMed	
	“Most recent” number of hits	“Best match” number of hits	“Most recent” number of hits	“Best match” number of hits
November 19, 2019	4697	5118	5116	5116
December 5, 2019	4714	4687	4685	4685

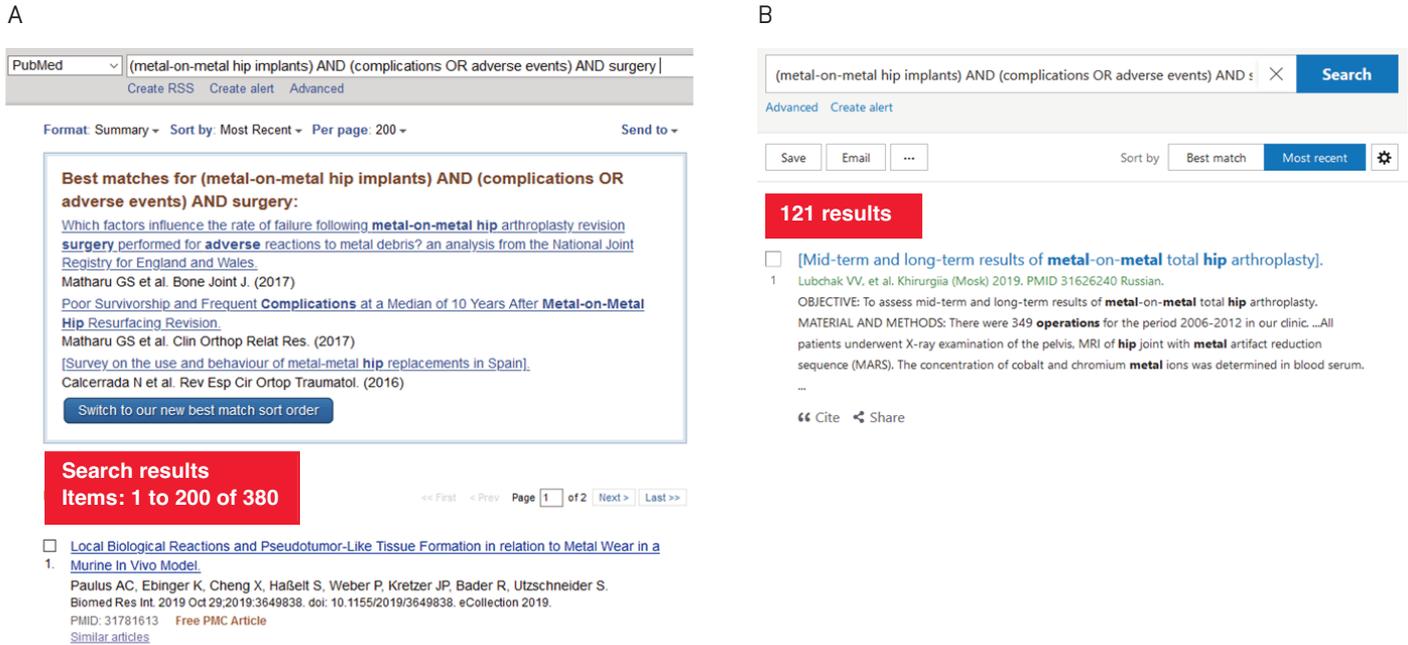


Figure 2. Database output. A, legacy version of PubMed. B, new version of PubMed. The very first search hit is displayed.

retrieval of sufficient and valid clinical evidence is especially crucial, as many assessments of hip implant conformity solely relied on publicly available clinical data from similar devices – a procedure that in some cases reportedly led to serious complications for patients.<sup>8,9</sup>

To assess the performance of both PubMed versions, a search for (metal-on-metal hip implants) AND (complications OR adverse events) AND surgery was conducted on December 18, 2019. Two different time frames (January 1, 2010, through December 31, 2015, and January 1, 2015, through December 18, 2019) were searched.

For the time period ranging from January 1, 2015, to December 18, 2019, without any additional limitation and employing the “most recent” format, the search string found 380 and 121 hits in the legacy and new version of PubMed, respectively (Figure 2).

Application of a time window from January 1, 2015, to December 31, 2015, delivered 189 hits in the legacy version and 49 hits in the new version of PubMed. Of these citations, only 43 were found in both interfaces. In contrast, 146 citations were returned only by the legacy version (Supplementary Table 4), and 6 were returned only by the new version (Supplementary Table 5). After reviewing the titles – and in some cases additionally the abstracts – of the identified citations, 98 of 146 (>65%) hits from the legacy

search and 5 of 6 (>80%) from the new interface search were considered as “potentially relevant”, indicating that the legacy version of PubMed identified a higher absolute number of relevant citations as compared to the new version of PubMed.

Similar results were obtained from the search for the second time period ranging from January 1, 2015, to December 18, 2019. Briefly, the legacy PubMed delivered 133 hits in total, whereas 62 of 133 hits did not appear in the parallel search with the new PubMed. Forty-three of the 62 publications were considered potentially relevant in the search context after assessment of the title (Supplementary Table 6). The new version of PubMed identified 85 hits in total, of which 14 were found exclusively by this search. All of those 14 publications as assessed by title were considered potentially relevant (Supplementary Table 7).

The two versions of PubMed translated the search terms differently, as shown below for the search of the period January 1, 2015, to December 18, 2019.

**Legacy version:**

(metal-on-metal[All Fields] AND (“hip prosthesis” [MeSH Terms] OR (“hip” [All Fields] AND “prosthesis” [All Fields]) OR

“hip prosthesis” [All Fields] OR (“hip” [All Fields] AND “implants” [All Fields]) OR “hip implants”[All Fields])) AND (“complications” [Subheading] OR “complications” [All Fields] OR (adverse [All Fields] AND events [All Fields])) AND (“surgery” [Subheading] OR “surgery” [All Fields] OR “surgical procedures, operative” [MeSH Terms] OR “surgical” [All Fields] AND “procedures” [All Fields] AND “operative” [All Fields]) OR “operative surgical procedures” [All Fields] OR “surgery” [All Fields] OR “general surgery” [MeSH Terms] OR “general” [All Fields] AND “surgery” [All Fields]) OR “general surgery” [All Fields] AND (“2015/01/01” [PDAT] : “2019/12/18” [PDAT])

**New version:**

(((((“metal-on-metal” [All Fields] AND (((“hip prosthesis” [MeSH Terms] OR (“hip” [All Fields] AND “prosthesis” [All Fields])) OR “hip prosthesis” [All Fields]) OR (“hip” [All Fields] AND “implants” [All Fields])) OR “hip implants” [All Fields])) AND (((((((((((“compl” [All Fields] OR “complicances” [All Fields]) OR “complicate” [All Fields]) OR “complicated” [All Fields]) OR

“complicates” [All Fields]) OR “complicating” [All Fields]) OR “complication” [All Fields]) OR “complications” [All Fields]) OR “complications” [MeSH Subheading]) OR “complications” [All Fields]) OR (((“adverse” [All Fields] OR “adversely” [All Fields]) OR “adverses” [All Fields]) AND ((“event” [All Fields] OR “event’s” [All Fields]) OR “events” [All Fields]))) AND (((((((((((((((((((((((((((((((“operability” [All Fields] OR “operable” [All Fields]) OR “operate” [All Fields]) OR “operated” [All Fields]) OR “operates” [All Fields]) OR “operating” [All Fields]) OR “operation’s” [All Fields]) OR “operational” [All Fields]) OR “operative” [All Fields]) OR “operatively” [All Fields]) OR “operatives” [All Fields]) OR “operator” [All Fields]) OR “operator’s” [All Fields]) OR “operators” [All Fields]) OR “surgery” [MeSH Subheading]) OR “surgery” [All Fields]) OR “operations” [All Fields]) OR “surgical procedures, operative” [MeSH Terms]) OR (“surgical” [All Fields] AND “procedures” [All Fields]) AND “operative” [All Fields])))) OR “operative surgical procedures” [All Fields]) OR “general surgery” [MeSH Terms]) OR (“general” [All Fields] AND “surgery” [All Fields])) OR “general surgery” [All Fields]) OR “surgery’s” [All Fields]) OR “surgerys” [All Fields]) OR “operation” [All Fields]) OR “surgeries” [All Fields])) AND 2015/1/1:2019/12/18[Date - Publication].

By mid-May of 2020, the new version of PubMed had become the default search interface. To investigate whether the new, default version of PubMed delivered identical search results as during the transitional period, the search for (*metal-on-metal hip implants*) AND (*complications OR adverse events*) AND *surgery* within the time frame ranging from January 1, 2010, to December 31, 2015, was repeated on June 10, 2019. The search retrieved 226 hits in total, exceeding the number of hits (49) found on December 18, 2019, more than fourfold. To determine whether the results included potentially relevant citations that were missed in the initial search performed on December 18, 2019, the search results were compared to those obtained by the legacy PubMed. In detail, the search identified 32 previously unrecognised publications (Supplementary Table 8 – including



22 relevant publications), rediscovered 6 publications that were found in the previous search by the new PubMed exclusively (Supplementary Table 5), and retrieved 188 of 189 citations found in the legacy PubMed. A single publication was still not identified in the new search: Chen, Zhongbo, Hemant Pandit, Adrian Taylor, Harinderjit Gill, David Murray, and Simon Ostlere. “Metal-on-Metal Hip Resurfacings – a Radiological Perspective.” *European Radiology* 21, no. 3 (March 2011): 485–91. Based on title and abstract, the publication could be relevant in the context of complications in MoM implants.

**Immunology/immunologic diseases**

Two independent searches (Immunology Search (Im) #1 and Im #2) with increasing complexity were performed to assess technical and layout features as well as database output among both versions of PubMed. Results are presented in the Supplementary Information section to provide initial insights towards technical features and database outputs based on searches with simplified search terms.

**Discussion**

PubMed is a commonly used search engine for identifying clinical data from scientific literature for multiple purposes. Specifically, the present investigation focusses on the needs in the medical device field, which relies on clinical evidence from scientific citations to accelerate the approval process of medical devices based on data obtained for equivalent/similar medical devices. Indeed, published clinical data from equivalent/similar devices provides supportive information to demonstrate safety and performance/benefits of the medical device – two main aspects assessed during the approval procedures. To ensure traceability, clinical evidence is gathered in a highly structured data identification process, as laid out, for example, in the guidance document MEDDEV 2.7/1 rev.4. The guidance document repeatedly asks for an ordered process intended to deliver identical search results. Moreover, the IMDRF technical documents on clinical evaluation (IMDRF MDCE WG/N56FINAL: 2019) and on clinical evidence (IMDRF MDCE WG/N55 FINAL:2019) apply, providing additional information on key elements and requirements for literature searches.

The recent release of the new version of PubMed by the NCBI raised immediate concerns regarding the traceability and reproducibility of search results. Thus, the main goal of the present investigation was to analyse the comparability of the search results retrieved by both versions of PubMed that were accessible in the period from November 2019 to June 2020.

The presented side-by-side comparisons reveal several differences between both PubMed versions. Visually, the 3-column illustration in the legacy version of PubMed was replaced by a 2-column layout. Moreover, information provided on the results page was altered, but still supplements the reader with sufficient detail. In addition, an excerpt of the abstracts is included in the displayed results, promoting a quick review of search results. Furthermore, the read-through incorporates snippets that are highlighted text fragments related to the search query to accelerate decision-making towards the relevance of a search hit.<sup>13</sup>

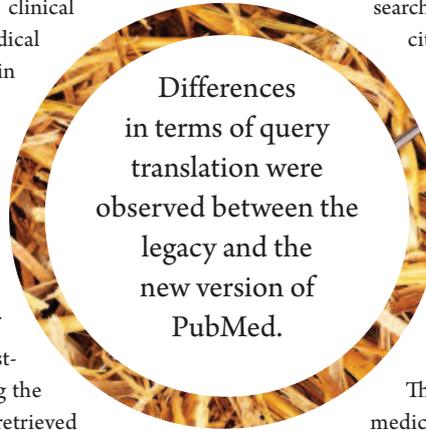
Column 1 as depicted in Supplementary Figure 1 contained a sidebar to further narrow down the search results. To ease the search processes, pre-set filtering options were provided by default. Although differences regarding the pre-set filtering option were evident, these could be quickly overcome by adding missing categories manually. Moreover, the elevated number of pre-set filtering options was an asset, easing immediate result sorting. Nonetheless, the sidebar does not allow filtering by date. Instead, the date range has to be inserted in the search field using the YYYY/MM/DD:YYYY/MM/DD[dp] format, which adds complexity to the entire search process.

Furthermore, filtering options on “journal categories” are somewhat restricted now as filtering by “core clinical journals” is no longer available in the new PubMed. Although this filtering option was discussed controversially among regulatory professionals, some users nevertheless applied this filter to narrow down the amount of search hits. However, limiting the search output created a bias towards high rank, high quality clinical publications only, leaving the possibility of missing relevant information published in journals that do not focus primarily on clinical data.

To review the traceability and reproducibility of search results, four different search scenarios were conducted covering different search terms as described in the Methods section. The chosen

search terms pertain to clinical sciences and to medical devices, respectively, in order to cover two major research fields that strongly depend on reliable data retrievability in PubMed. The major finding across searches was that the legacy and new version of PubMed yielded inconsistent search results affecting the overall reliability of retrieved clinical evidence. Briefly, the legacy version of PubMed found more relevant publications than the new platform during the transitional period until May 2020. The New PubMed Transition FAQs webpage provides some valuable insights regarding the observed inconsistencies.<sup>14</sup>

Entered search terms were translated by PubMed’s automatic term mapping.<sup>15</sup> The new version of PubMed appeared to massively use automated term mapping. Apparently, the new search adds synonyms, truncations, plurals, verbs, and British/American spelling variants to the translated search query. Of note, the review of translated search queries included misspellings like “antibodie”, “antibodys” or “ventillation”. The NCBI stated that the procedure aims to cover all publications as originally submitted by the publisher. Thus, although misspelled, all words deliver results. Moreover, the new version of PubMed takes advantage of an updated technology for document indexing, storage, and retrieval.<sup>13</sup> Although we had anticipated that the technical refinements would result in an increased number of search hits, in most cases decreased numbers of hits were observed in the new version as compared to the legacy version during the transitional period. Of note, a search performed in June 2020 after the new version had become the default search interface, delivered more hits than an identical search performed during the transitional period in December 2019, indicating a continued update and improvement process. Further, after the new PubMed became the default search interface, 32 previously unrecognised, potentially relevant publications were identified covering the entire search period selected for the query. Intriguingly, these 32 publications were not retrieved using the legacy version of PubMed indicating that the previous



search would have missed relevant citations. Moreover, in the presented search scenario the new, default PubMed failed to deliver one potentially relevant paper, that was found by the legacy PubMed only. These findings already pointed to a limited comparability between both versions of PubMed.

Thus, with regard to the medical device field, it must be advised to clearly indicate the version of PubMed that was used during the clinical evidence collection process and at what point during document updates the switch to the new PubMed version was made.

PubMed offers two alternative sorting methods “most recent” and “best match”. For the legacy version of PubMed, the number of hits varied between both methods, whereas the output from the new platform is identical for both sorting methods. According to information provided by the PubMed help desk, in the new PubMed, “best match” and “most recent” rely on the same platform, and retrieve the same results, which then are ranked differently, according to the selected sort order. With the legacy PubMed, only searches sorted by “best match” were taking advantage of the environment now utilised in the new PubMed. Therefore, the number of results between “best match” and “most recent” could be slightly different.

In legacy PubMed, the “best match” sort order is based on an algorithm analysing every single PubMed citation found with entered search terms. For each search query, “weight” is calculated for citations depending on how many search terms are found and in which fields they are found. In addition, recently published articles are given a somewhat higher “weight” for sorting. The top articles returned by the “weighted” term frequency algorithm are then re-ranked for better relevance by a machine-learning algorithm.

The new relevance ranking algorithm combines over 150 signals that are helpful for finding best-matching results. Most of these signals are computed from the query-document term pairs, e.g., number of term matches between the query and the document, while others are either specific to a document, e.g., publication type; publication year, or query, e.g., query length

(personal communication with National Library of Medicine Support, June 4, 2020).<sup>16</sup> Importantly, the “best match” sorting is not designed for comprehensive or systematic searches (personal communication).

Differences in terms of query translation were observed between the legacy and the new version of PubMed. Of note, inserting the search string generated by the new version of PubMed into the search bar of the legacy version did not deliver similar results as compared to the new version, indicating that it was not only the search term translation process that was updated. Indeed, the new PubMed employs an updated search syntax that might lead to variable numbers of search hits compared to the legacy platform.<sup>14</sup> Nonetheless, both versions of PubMed identified a substantial set of overlapping citations. However, additional literature was found by either search engine pointing to an obvious inconsistency. Importantly, the issue was reduced with the new, default PubMed, but not resolved completely. Thus, PubMed users from the regulatory field are advised to use PubMed with caution to not hamper the approval process. Useful combinations of search queries, as they are typical in such searches, should be employed and search strings should be designed with possible synonyms in mind. Moreover, to present a comprehensive state-of-the-art overview based on all the available literature, users from the regulatory field should consider the use of a second literature database.

In an email conversation with the National Library of Medicine (January 2020), it was confirmed that “the new PubMed is under active development, and features will be introduced and updated on a regular basis as we continue to enhance the system”. Indeed, improved search functionalities such as wildcards, groupings and joins have been implemented in the new version of PubMed. The wildcard search will be no longer limited to 600 variants.<sup>13</sup>

Overall, unstable database output might occur in the near future until feature development and usability testing has been completed successfully and the final version of the new

PubMed has been rolled out. From the NCBI’s blog entry and FAQ page it is obvious, that the new version of PubMed will be subject to further changes in the short and long term.<sup>5,14</sup> It is highly likely that these amendments will further affect the quantity and quality of search results and also will make retrospective comparisons more difficult. Together, the presented observations and comments/replies from the NCBI suggest that the new version of PubMed will potentially be updated constantly and thus over time might deliver alternating results.

Thus, the use of the new version of PubMed to re-retrieve clinical evidence obtained using the legacy site for CE approval processes must be considered with caution. Although the new PubMed is set as default, the legacy PubMed is accessible at <https://pmlegacy.ncbi.nlm.nih.gov/> at least until end of September 2020. Furthermore, a search strategy in alignment with PubMed’s new common practice must be developed in the meantime, and it is recommended to clearly identify and disclose the version of PubMed applied during the transition period from old to new interface. Moreover, under special circumstances, it might be advisable to double check the automated term mapping and combine searches in both versions to draw comprehensive conclusions and avoid missing important literature for approval processes. In addition, a parallel search in a second literature database such as LIVIVO or the Cochrane Library may retrieve missed citations by PubMed providing a fuller picture of the scientific landscape pertaining to the subject medical device.

## Conflicts of interest

The authors declare no conflicts of interest.

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# Ethical challenges in acknowledging professional writing support

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## Abstract

Professional medical writers have an important role in facilitating the accurate and timely dissemination of medical and scientific data. This support should be appropriately acknowledged in peer-reviewed publications, but guidance on how to appropriately disclose and attribute the contributions of individual medical writers is lacking, limiting transparency in the publication development process. In particular, the contributions of

subcontracted or freelance professional medical writers are inconsistently acknowledged. We propose personally acknowledging any professional medical writer who makes a substantial contribution to the outline or full first draft of a publication or who provides a substantial intellectual contribution to publication development. This will provide appropriate and transparent attribution of the contributions made by medical writers to manuscript development.



## Introduction

The role of professional medical writers in supporting the accurate and timely dissemination of medical and scientific data in peer-reviewed literature is now widely recognised, and formal guidelines on attribution, acknowledgement, and authorship (when justified) for professional medical writers have been issued.<sup>1,2</sup> These guidelines are clear in the responsibilities of professional medical writers and the need for appropriate disclosure of their contributions. However, applying these guidelines can be challenging, especially when writing tasks are subcontracted or delegated to freelance writers who are not directly employed by a medical communications agency because the criteria defining who to acknowledge, and how, are lacking.

**What constitutes writing assistance that is deserving of acknowledgement remains undefined.**

### Why should professional medical writers be personally acknowledged?

The International Committee of Medical Journal Editors (ICMJE) criteria govern authorship and the Good Publication Practice 3 guidelines have outlined the role of professional medical writers working on industry-funded research.<sup>1,2</sup> However, there is currently no guidance on ethical publication practices for subcontractors or an industry code of conduct regarding subcontracting medical writing services. The conventional practice in acknowledging medical writers is to name the professional medical writer(s), the organisation they are employed by and the source of funding for their assistance in the Acknowledgements section of manuscripts.<sup>1</sup> This aims to avoid accusations of ghostwriting, which has been defined as “the unacknowledged

use of writing assistance”,<sup>3</sup> but what constitutes writing assistance that is deserving of acknowledgement remains undefined. In practice, this means that substantial medical writing support provided by subcontractors or freelancers, for example, may not be acknowledged. Instead, contributions are often exclusively credited to agency staff.

## How should professional medical writers be personally acknowledged?

Stocks et al. provided narrow examples of contributions that would qualify a medical writer to be acknowledged, such as drafting the introduction and discussion sections of a manuscript or developing a manuscript from a clinical trial report written by another writer with substantial input from the authors, but without performing a literature review or elaborating on the discussion.<sup>4</sup> We believe that a broader framework must be defined to facilitate a consistent standard. Namely, individual professional medical writers should be personally acknowledged if they have:

- Made a substantial contribution to drafting the outline or full first draft of a publication; or
- Provided a substantial intellectual contribution to publication development.

Individuals providing subcontracted or freelancer professional medical writing support who meet the criteria outlined above should also be acknowledged using the following statement: “[Name of subcontracting individual] of [Contracting medical communications agency] provided professional medical writing support funded by [Sponsor].”

This statement aims to provide greater transparency by appropriately attributing credit to individual subcontracted writers, while also crediting the contracting party by naming them as the entity supplying medical writing support.

## Increasing transparency surrounding medical writing support

Potential conflicts of interest are rarely discussed between subcontractors and agencies. Situations do occur where freelance writers are simultaneously working on projects relating to competing drugs (sometimes with the full knowledge and blessing of at least one client), in contrast to

Professional medical writers should have the right to claim responsibility for their work, much as an artist or photographer receives credit for a commissioned piece.

the agency setting where clients demand and expect rigid controls between colleagues working on conflicting accounts. Acknowledging the support of individual subcontractors in the literature would provide greater transparency by ensuring public disclosure (and discoverability) of potential competing interests medical writers may have.

## The right to benefit from intellectual exercises

Denying the opportunity for contributors to approve submissions is a potential loophole that has been identified in the ICMJE criteria for authorship that could be used to inappropriately avoid granting authorship to an individual.<sup>6</sup> This same loophole applies to professional medical writers, especially subcontractors or freelancers who may be exploited, in that acknowledgement may be disproportionately or solely attributed to a supervising writer. Furthermore, the passing of time, rather than lack of intellectual contribution, may be used to justify not contacting a subcontracted or freelance writer to seek permission for acknowledgement at the time of manuscript submission.

Professional medical writers are also routinely expected to indemnify their clients against errors and omissions as part of the manuscript development process. In return, they should have the right to claim responsibility for their work, much as an artist or photographer receives credit for a commissioned piece.

Reports from more than 15 years ago also describe successful attempts to interrogate the Acknowledgements sections of published scientific literature to better understand the intellectual contributions of individuals to publications.<sup>7</sup> Efforts to assess the contribution of individuals to the scientific body of knowledge outside of authorship have continued since, such as Publons collating peer review contributions. Accordingly, for many professional medical writers, acknowledgement is a formal recognition of their contribution to the scientific literature and a demonstration of their skill. Appropriate acknowledgement for a medical writer has implications for their career advancement; therefore, the impact of novel tools being used to assess contributions to the scientific literature (beyond authorship) must be considered.

## Increasing the accountability of medical writers

Informal survey data indicate that only 3% of professional medical writers would decline acknowledgement.<sup>5</sup> Before an individual is acknowledged in a manuscript, the ICMJE recommends seeking written permission because acknowledgement implies endorsement of the content in a manuscript and the policies and procedures followed during drafting.<sup>2</sup> Therefore, the ability to decline acknowledgement is an important mechanism for self-regulation within the industry.

While the default position may be that a subcontractor should be acknowledged, any ability to disagree with, influence and/or protest client practices is generally limited, so declining acknowledgement offers one method of balancing what can be a one-sided working relationship in the client's favour. Accordingly, subcontractors should not be forced to accept responsibility for outputs or practices that they do not agree with.

## Conclusions

There is limited guidance on how to assess the contributions of individual professional medical writers to manuscript development or define who should be acknowledged when disclosing medical writing support. This is particularly relevant when medical writing supported is subcontracted, or performed by a freelancer, without attribution to the individual writer. Accordingly, we propose criteria for identifying and appropriately acknowledging all professional medical writers who have made substantial contributions to manuscript development.

## Conflicts of interest

BH is the owner and Managing Director of Kainic Medical Communications Ltd., a company that provides subcontracted medical writing support to medical communications agencies. BH is also a principal consultant at First in Human, the specialist pharmacokinetics/ pharmacodynamics division of Kainic Medical Communications. MS is an

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For many professional medical writers, acknowledgement is a formal recognition of their contribution to the scientific literature and a demonstration of their skill.

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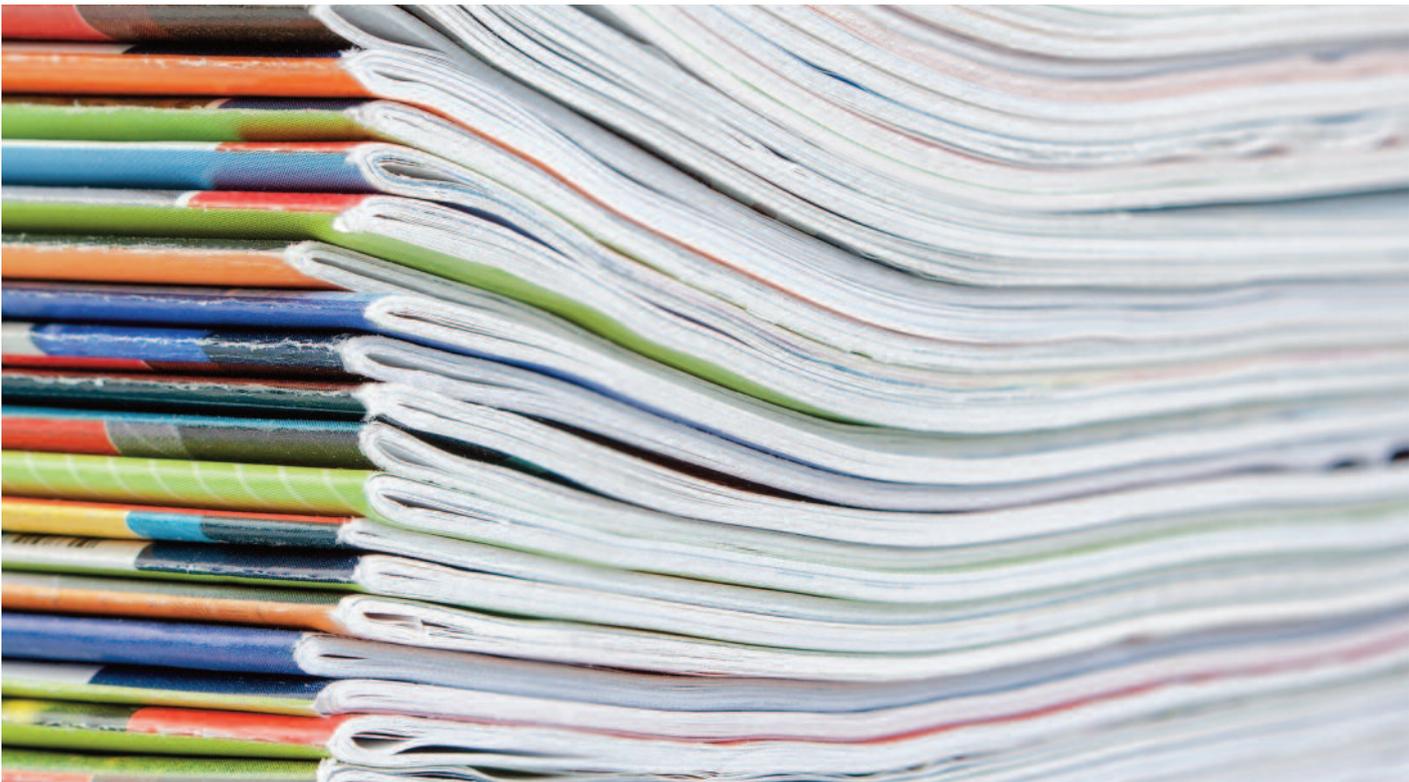
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# Publication management software for medical writers

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## Abstract

Managing a complex publication plan for several products or indications with overlapping timelines can be challenging. Publication management software solutions are available to support the medical writer in planning, writing, approving, and disseminating scientific publications. Key features of these programs include design and approval of a publication plan, verification of author eligibility, assignment of medical writing resources and authors, management of

document reviews, auditing of author contributions, and ensuring compliance with industry standards, transparency requirements, and standard operating procedures. Some software packages provide data visualisation tools to track performance, budget spent, and author engagement. Medical writers supporting publications should become familiar with software features to improve efficiency in managing and writing scientific communications.

The pharmaceutical industry is committed to publishing clinical study results, irrespective of whether they are positive or negative.<sup>1</sup> By disseminating scientific data, as abstracts, posters, presentations, or manuscripts, pharmaceutical companies meet ethical guidelines, industry standards, and corporate compliance requirements.<sup>2,3</sup>

## Publication planning

A publication plan is a product-specific strategic document that evolves over a product's lifecycle according to the stage of research. It is generally developed and executed by the medical affairs department in collaboration with cross-functional stakeholders. The publication plan specifies how the communication will be delivered (e.g., poster, manuscript, presentation, or video content), what audience will be targeted (e.g. payer, healthcare provider, patient), what the content will be, and what the strategic messages will be. Key messages may be defined according

to the research conducted, competitor analysis, or gaps in published literature. Deciding where to present research can depend on the type of research conducted, the audience to be targeted, the type of publication, and journal metrics (impact factor, publication lead times, and rejection rate).<sup>4</sup>

**A publication plan is a product-specific strategic document that evolves over a product's lifecycle according to the stage of research.**

In addition to the well-established role of the medical writer in authoring content and managing reviews of publications, medical writers are often consulted to contribute to the strategic publication plan. However, managing a publication plan for multiple products or indications with overlapping timelines can be challenging. An integrated software solution can help design, approve, and implement a publication plan, verify author eligibility, assign resources and reviewers, manage document reviews, audit author contributions, and ensure compliance with Good Publication Practice guidelines, transparency requirements, and

standard operating procedures.

In this article, I present key features of three proprietary software solutions designed to support company-sponsored publication plans (Table 1).

### The PubSTRAT suite

The PubSTRAT suite (Anju Life Sciences Software) is an integrated software solution comprising several web-based applications covering publication planning, writing, document management, and citation. These solutions include JSCA (Journal Selector and Conferences Authority), SYQUENCE (an information life-

cycle management platform), PubSTRAT (Publication Project Management Application), and Cite Central (a citation and knowledge repository). These individual platforms may be purchased separately or as a single integrated solution.

### JSCA

JSCA, a journal and conference database that includes more than 2,500 journals and 1,500 conferences (and 600,000 abstracts), can be used to design a publication plan. Users can search the platform by MeSH (Medical Subject Heading) term and can access a list of journals, a citation count, journal impact factors, Eigenfactor scores, and journal selection criteria. Crucial information that assists in publication planning includes the estimated time from submission to acceptance and time from acceptance to publication. Selection criteria for conference acceptance are also included and are updated daily as the conference date approaches. Analytic features include the number of articles published by journal per topic/MeSH term within a given timeframe, which can be presented in both in tabular and graphical formats. Future updates will include an abstract library sourced from the JSCA database.

Table 1. Key features of publication management software

Feature	PubSTRAT	Datavision®	PubsHub™
Author publication management	X	X	X
Real-time review	X	X	X
Document audit trail and version history	X	X	X
Configurable email templates and notifications	X	X	
Journal and conference database	X	X	X
Publication planning software	X	X	
Project wizard	X	X	
Configurable timeline templates	X	X	
Data visualisation module	X	X	
Publication repository	X	X	X
Veeva Vault integration	X	X	X

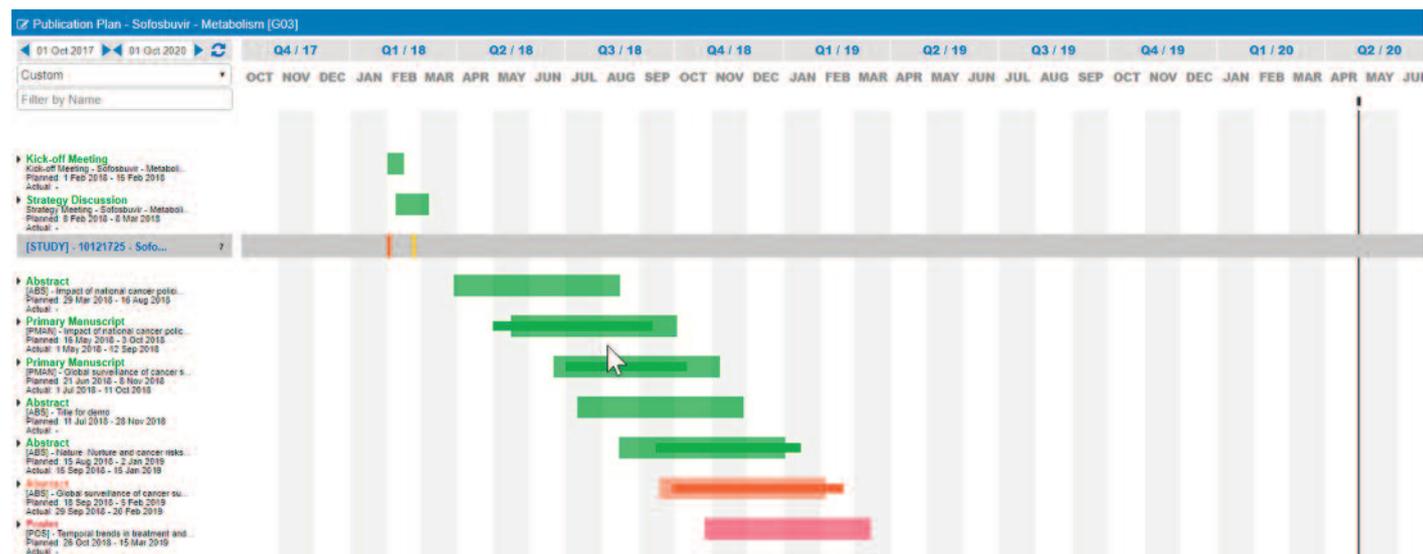


Figure 1. Publication plan Gantt chart: SYQUENCE (PubSTRAT)

In SYQUENCE, publications by project and type are presented vertically. The timeline for each project is shown horizontally on a Gantt chart by quarter, month, and year. The colour coding describes the project status: red indicates pending, orange indicates active authoring, and green indicates published. Projects can be filtered by project name or timeframe.

PROJECT ID	REQ	DUE DATE	TASK	PRODUCT	PROJECT	ACTIONS
40463	*	6 Aug 2021	Author Invitation	Mopesalot	MOPE-O1234 ABS Malloy/ISAD 2022 : 11th Biennial Conference of the International Society for Affective Disorders PUT SHORT TITLE HERE 40463	
40459	*	9 Dec 2020	Submission	Mopesalot	MOPE-O4552 ABS Malloy SDPA 2020 : Annual Summer Dermatology Conference of the Society of Dermatology Physician Assistants PUT SHORT TITLE HERE 40459	
40459	*	8 Dec 2020	Incorporate final changes/prepare for submission	Mopesalot	MOPE-O4552 ABS Malloy SDPA 2020 : Annual Summer Dermatology Conference of the Society of Dermatology Physician Assistants PUT SHORT TITLE HERE 40459	
40459	*	4 Dec 2020	Final sign-off	Mopesalot	MOPE-O4552 ABS Malloy SDPA 2020 : Annual Summer Dermatology Conference of the Society of Dermatology Physician Assistants PUT SHORT TITLE HERE 40459	
40459	*	27 Nov 2020	Internal and Author review, Draft 1	Mopesalot	MOPE-O4552 ABS Malloy SDPA 2020 : Annual Summer Dermatology Conference of the Society of Dermatology Physician Assistants PUT SHORT TITLE HERE 40459	
40459	*	18 Nov 2020	Incorporate Reviewer/Author changes to Outline	Mopesalot	MOPE-O4552 ABS Malloy SDPA 2020 : Annual Summer Dermatology Conference of the Society of Dermatology Physician Assistants PUT SHORT TITLE HERE 40459	
40459	*	18 Nov 2020	Incorporate changes to Draft 1	Mopesalot	MOPE-O4552 ABS Malloy SDPA 2020 : Annual Summer Dermatology Conference of the Society of Dermatology Physician Assistants PUT SHORT TITLE HERE 40459	

Figure 2. Publication management page: PubSTRAT

In the publication management page of PubSTRAT, tasks can be filtered by product, due date, or project. Projects can also be accessed by status on separate tabs (“To Do”, “Planned”, and “Done”). By clicking the task, users can view this task in the overall timeline. By clicking the project name, users can view project details shown in the project page. By clicking on the icon in the Actions column, users can delegate a task to a specific person.

### SYQUENCE

The SYQUENCE application enables users to create the publication plan in an electronic format and to circulate it for approval by a steering committee or leadership. SYQUENCE captures tactics (strategic recommendations) for a study or product, including the focus of communication, the target audience, and key dates and milestones. This allows for publication tactics to be mapped on a timeline (Figure 1). Once the plan is approved in SYQUENCE, each tactic is automatically synched with PubSTRAT as a separate project.

### PubSTRAT

PubSTRAT integrates publication planning and workflow management for internal and external authors through a cloud-based application. System access can be configured by user type (e.g., project manager, medical writer, or reviewer). Users can create and manage projects in PubSTRAT and assign tasks for project contributors to execute. Details of the scope and audience for each journal or congress targeted in the publication plan are hyperlinked in PubSTRAT.

PubSTRAT provides templates for generating author invitations, author agreements, and electronic checklists for meeting authorship requirements, and it can capture digital signatures.

As such, PubSTRAT can be used to audit author engagement and demonstrate compliance with Good Publication Practice guidelines and corporate integrity agreements.

Publications can be viewed from a publication management page (Figure 2). Further details for each publication, including the target journal, lead author, corresponding author, assigned medical writer, and active tasks, can be viewed from a project page. Managers can assign medical writers to a project, which will trigger an automated email to the writer. Workflows are created according to the timelines allocated in configurable project timeline templates, which include document development, review, and approval steps. Workflow subtasks may be delegated to other authors or reviewers. Additionally, based on the timelines in the workflows, automated reminder messages for authors are triggered. The platform allows for online document writing, simultaneous document review, and approval by internal and external authors. PubSTRAT includes suggested timelines by deliverable (e.g., abstract, poster, manuscript), which can be configured to meet the client needs.

To help oversee the publication process, data visualisation tools are available, including performance metrics (e.g., publications accepted, cancelled, in progress, pending finalisation, and

rejected) and budgeting tools (e.g. budget spent and remaining).

### CITE CENTRAL

CITE CENTRAL is a centralised web-based repository for citation information and final documentation for documents created in PubSTRAT. It creates automatic citations and consolidates a product bibliography, and it can be used to disseminate publications to internal and external stakeholders.

### Datavision®

Datavision (Envision) is a web-based software platform that integrates a journal and congress database of over 7,000 journals and 27,000 congresses, a publication planning module, a document management system, and a scientific communication platform.

### Scientific communication platform

The scientific communication platform allows companies to load themes, key communication points, and supporting statements into the system and then visualise how the publications align with the publication plans. Optional features that may be purchased separately include an enterprise content management library that allows publications to be captured, managed, archived, and distributed; finance and budgeting

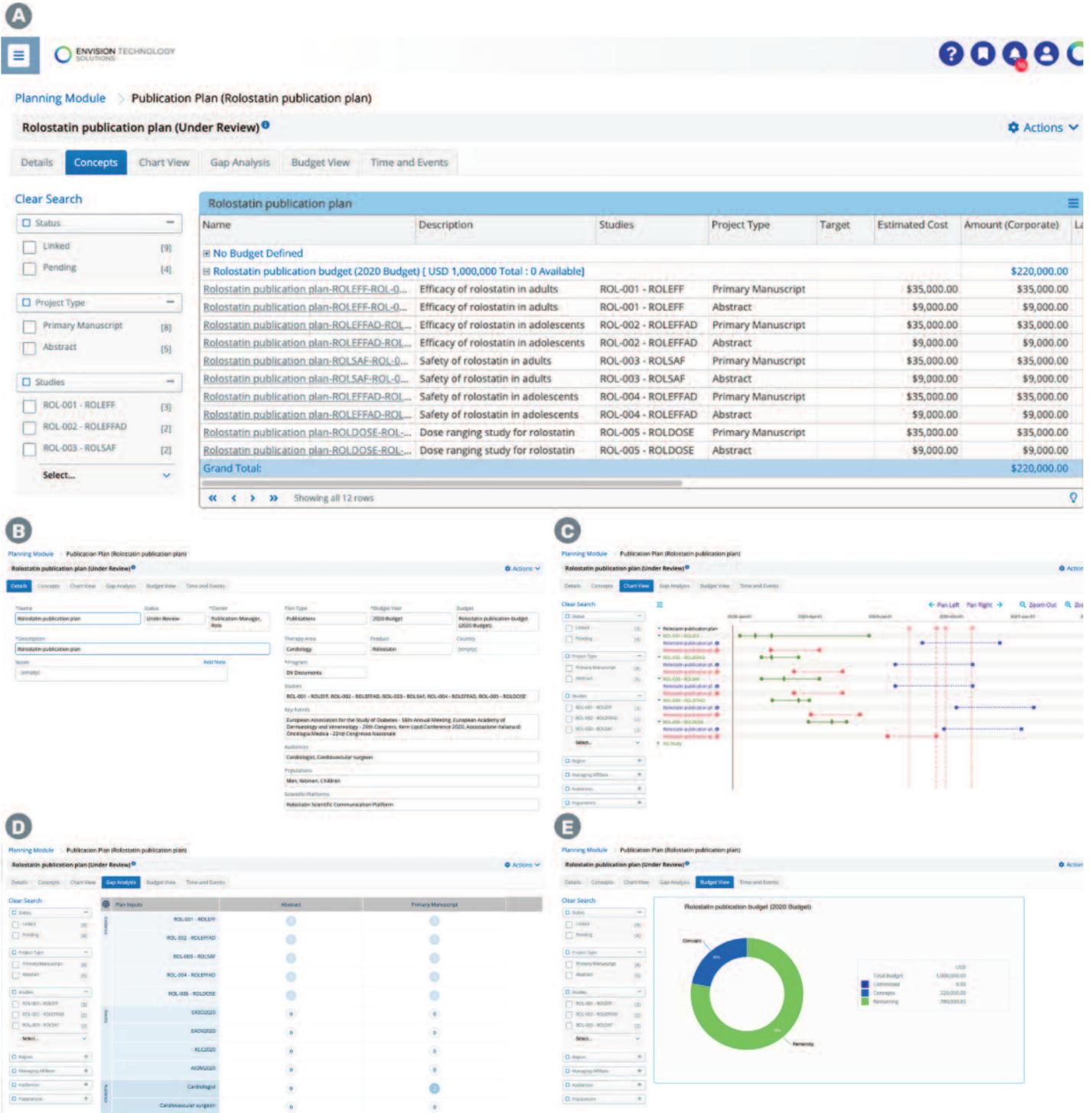
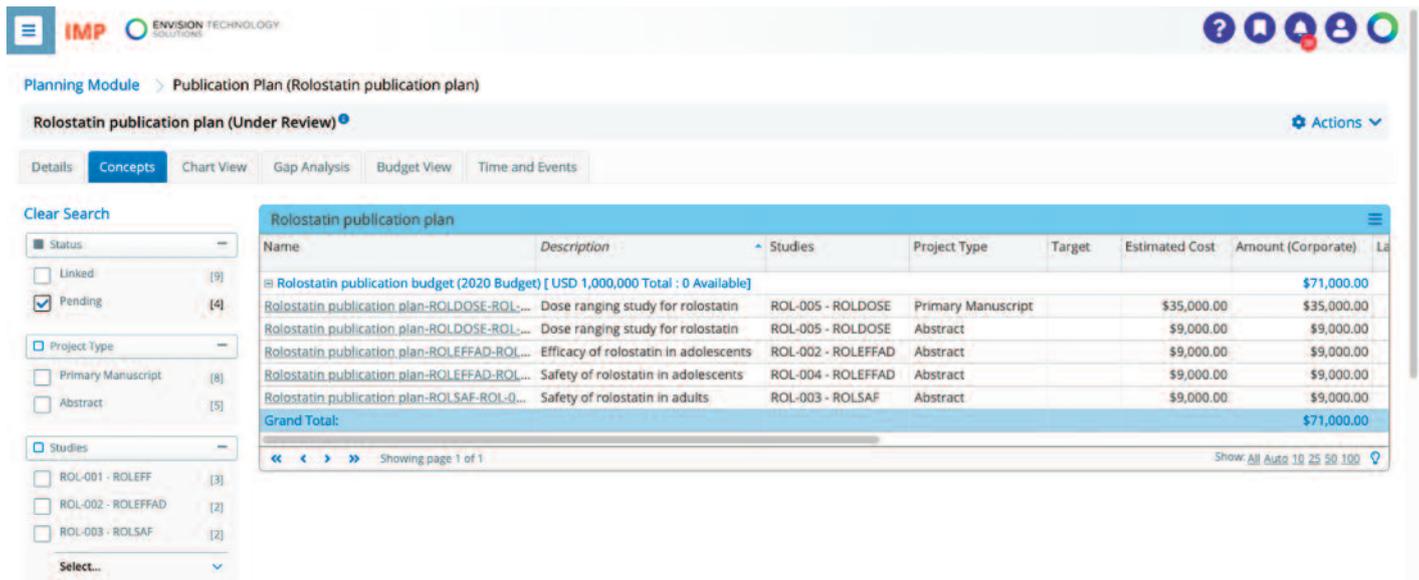


Figure 3. Publication plan: Datavision

- A. The Concepts tab of the publication plan shows a list of planned projects included in the publication plan.
- B. The Details tab, which provides the studies and other inputs upon which the publication plan is based.
- C. The Chart View tab shows a Gantt chart of projects included in the publication plan.
- D. The Gap Analysis view provides the planned publications by audience and tactic versus the plan's inputs; for example, the input for the congress EASD2020 shows that no abstracts are planned (indicated by the circle with an embedded zero).
- E. The Budget view shows the allocated budget vs. budget spent by project.



**Figure 4. Publication Plan Concepts list: Datavision**

The Publication Plan Concepts list in Datavision includes a summary list of concepts (also known as tactics or strategic recommendations) included within the publication plan. Users can click the hyperlinked project name to retrieve further details of the study included in each project, such as the first subject first visit, last subject last visit, publication type and audience, project timelines, and linked statements about the data to be relayed to appropriate external audiences.

tools; automated healthcare provider debarment checks; and an enhanced scientific communication platform.

### Publication planning module

In the publication planning module, a wizard can be used to design a publication plan that specifies tactics; audiences, journals, and congresses; and potential differences between the plan and the communication objectives (Figure 3). The module provides metrics from the journal and congress database, including the overall acceptance rate, the size and nature of their audience, and, for journals, the impact factor, Eigenfactor score, and types of articles published. A consolidated publication plan can be viewed from a summary list. (Figure 4).

The publication plan can be circulated, reviewed, and approved in Datavision. Datavision converts the details of the publication plan into a PDF for review and approval. Reviewers will receive a notification that includes a link to the publication plan review. They can comment on the publication plan using embedded review software. Comments are stored in Datavision. Once it is approved, based on the type of communication (e.g., abstract, poster, manuscript, presentation) and submission deadline, the platform will generate a proposed

timeline that may be viewed from a project management page (Figure 5). Since Datavision integrates with clinical trial management systems that capture study timelines, Datavision can be used to highlight the required changes to milestones in the publication plan if study dates change.

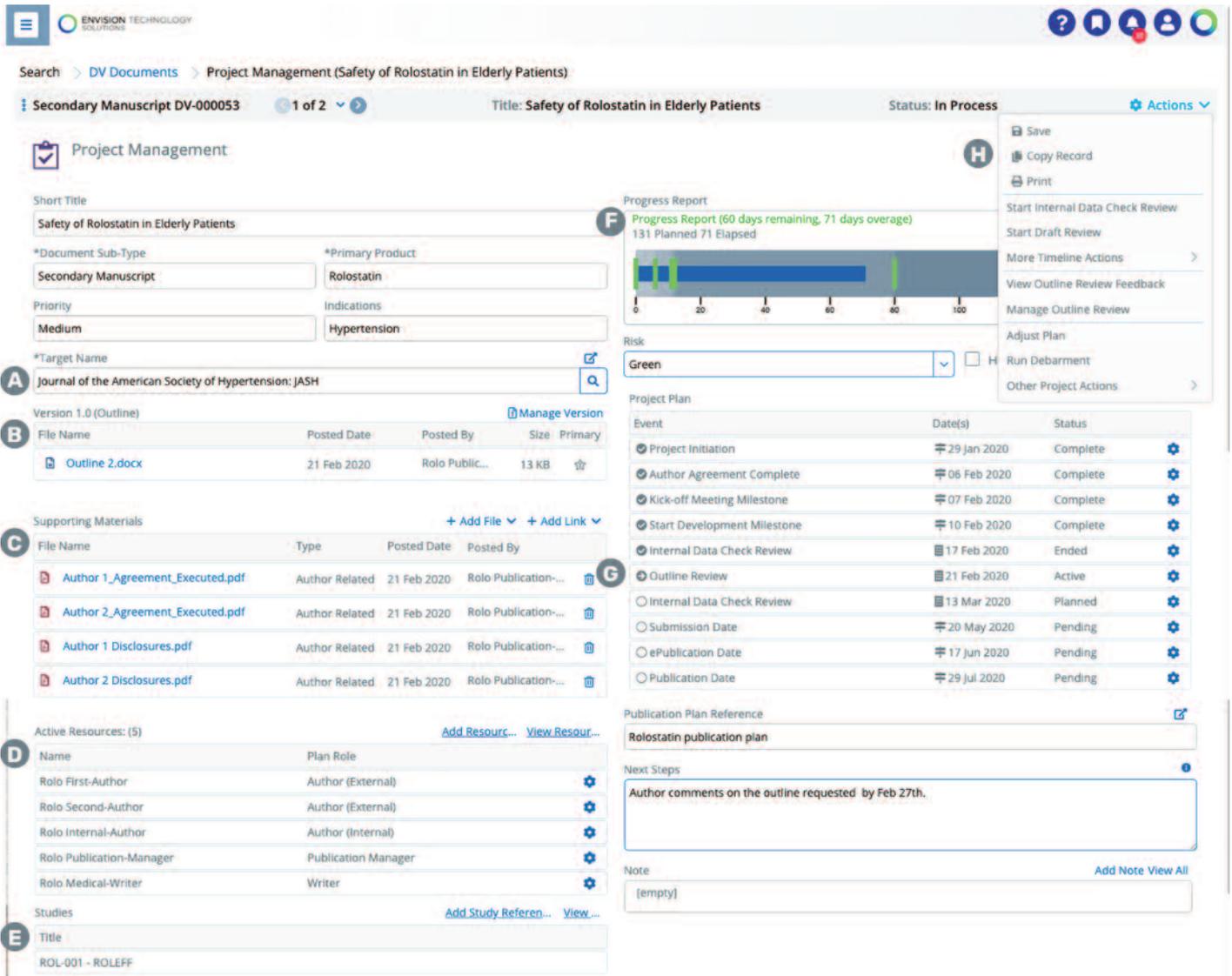
Internal and external authors may be assigned to a project in Datavision. Author permissions, including the reports and dashboards they have access to, are configurable. Electronic signatures (through DocuSign®) and electronic capture of conflicts of interest and disclosures can be completed in Datavision. To confirm authorship eligibility, the platform also features an automated debarment check (i.e., proposed authors have been excluded, suspended, or otherwise ineligible to participate in Governmental health care programmes).

Managers can use the software to assign a medical writer, which will trigger an email to the writer. Medical writers will interact with Datavision via a workbench view, which is a consolidated list of assigned projects and current and future tasks to perform. Medical writers can manage author review and approval workflows from this page. Automated reminders are triggered according to predefined but configurable timelines. Supporting documents may be stored

for author access during review. By the third or fourth quarter of 2020, functionality for simultaneous review by multiple reviewers will be enabled using doDOC (doDOC.com), a real-time co-authoring tool.

To provide managers with oversight of the status of the publication, reporting tools are available for document review metrics and budget planning. An at-a-glance view of progress against the publication plan and project milestones is displayed on a Gantt chart. A dashboard view (Figure 6) provides high-level metrics by project, a document timeline, publication plan metrics, and a list of outstanding tasks. Reports can be configured, saved as templates, and exported. Additional analytic features for further data visualisation include integration with the data analytics platform QlikView® and the ability to export to other business analytics tools (e.g., SAP BusinessObjects, Tableau, and Sisense).

To enable company-wide or role-specific distribution, once publications are finalised, they can be pushed from Datavision into a document library or another third-party document repository (e.g., Veeva Vault), which can be used to store, manage, and distribute regulatory and clinical trial documentation. For each publication, a count of citations is displayed. The enterprise content management library can be



**Figure 5. Project Management page: Datavision**

In the Project Management page of Datavision, the project manager can manage each publication. The left side of the page shows (A) document details, including the target journal or congress, (B) the document version, (C) a link to supporting materials (e.g., tables, listings, literature references) to be used in review and quality control, (D) the author list, and (E) a link to the study in the study database. On the right side of the page, (F) the project plan is presented by timeline, and (G) timeline step. Using the Actions dropdown menu (H), the project plan milestones can be updated and the document can be sent for review and approval.

used to develop and distribute a bibliography of suggested reading materials.

### PubsHub™

PubsHub (ICON) is web-based integrated publication planning solution comprising a database of medical journals and scientific congresses (Journals & Congresses), software for publication planning and management (PMSolution),

and a publication repository (Knowledge Manager). The software may be purchased as an integrated solution or as separate modules. A subscription to PMSolution includes access to Journals & Congresses.

#### Journals & Congresses

Journal & Congresses is a publication planning research engine that provides key data points for

over 4,600 journals, 3,500 congresses, and 4,000 professional scientific associations, spanning more than 100 medical and scientific therapeutic areas. Key metrics for journals and congresses can be compared (Figure 7). Content is updated on an ongoing basis. Predatory journals and congresses are flagged and excluded from the database. Information for journals includes the impact factor, circulation, readership, rejection



Figure 6. Publication Manager dashboard: Datavision

In the Publication Manager dashboard of Datavision, the left side of the dashboard provides (A) links to recent documents accessed, as well as outstanding tasks, (B) a project status summary, and (C) pie charts showing projects by type and status. On the right side of the dashboard, (D) project managers can include alerts or other general information to be viewed by Datavision users and (E) display summary metrics for publication status in a bar chart. In (F) a comparison of actual timelines (in dark green) and projected timelines (grey) is also presented.

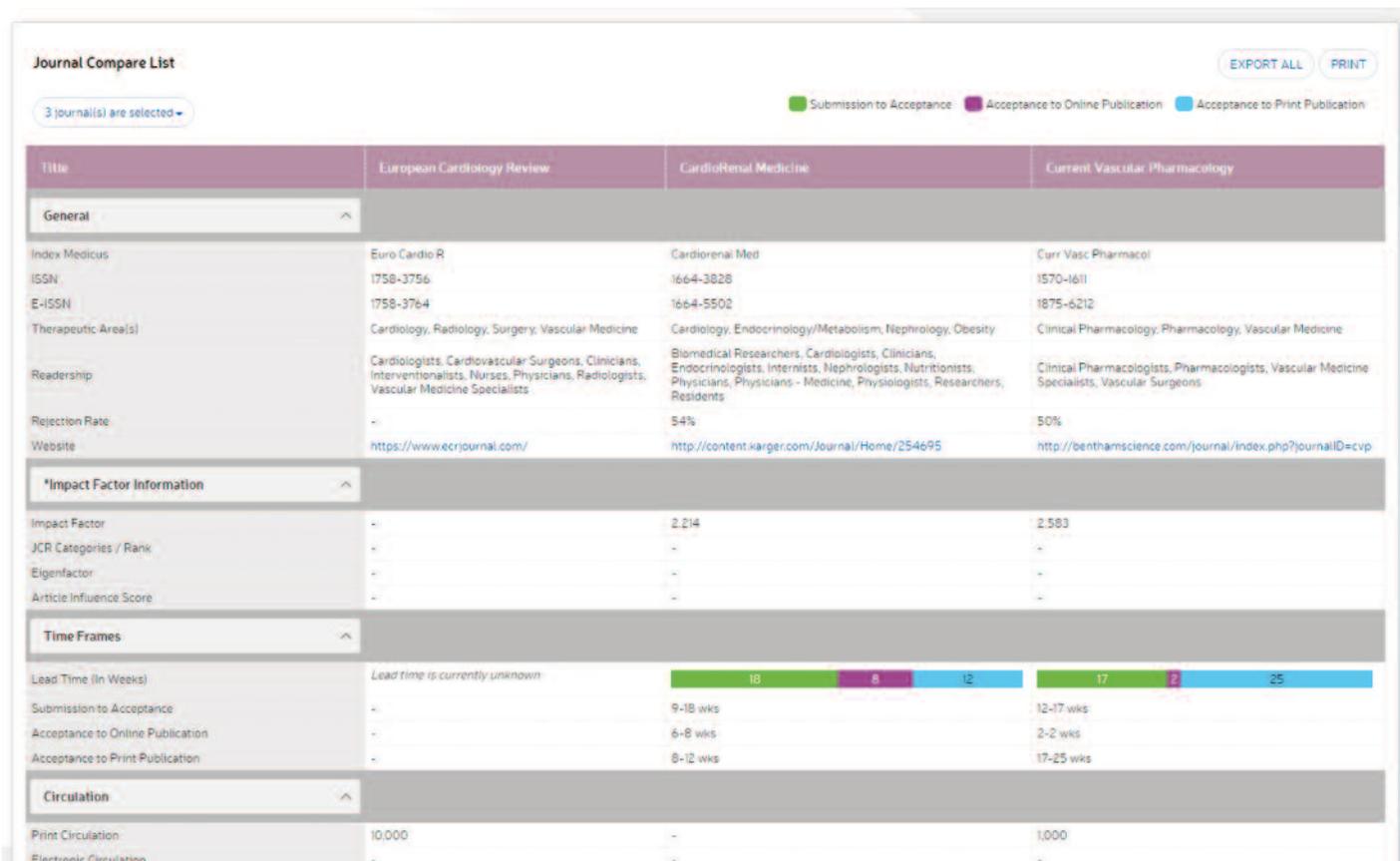


Figure 7. Journal Compare features (Journals & Congresses) PubsHub

The Journals and Congresses database of PubsHub provides a comparative view of journal metrics key to publication planning, including rejection rate, impact factor, and circulation. Timelines from submission to print publication are colour coded as green for submission to acceptance, purple for acceptance to online publication, and blue for acceptance to print publication.

rate, submission timeframes, restrictions on “encore” publications, and submission guidelines. For congresses, deadlines and the availability of extensions are provided.

**PMSolution**

PMSolution is a software platform for project management and collaborative document review that provides an audit trail for author involvement. It has two modes of operation for document review: a traditional workflow and “CoAuthorLive”.

In the traditional workflow, after initiating a review, reviewers receive an automated email containing a link to access the document. Reviewers can sequentially access, edit, and upload a revised copy of the document. Reminder emails to reviewers are manually triggered. CoAuthorLive allows real-time simultaneous review by multiple reviewers.

Key metrics (e.g., adherence to timelines by reviewers) are displayed on dashboards if meta-

data are added to the document. A forthcoming update to the platform includes enhanced analytic capabilities and data visualisation.

Medical writers and project managers can access and view the current status of projects via a user-specific project dashboard (Figure 8). Security features are available to limit functionality and access by user type. To facilitate project creation, a “copy project” feature enables replication of project information, metadata, supporting documents, and team members. Lastly, PMSolution can track payments to authors.

PMSolution can be integrated with Veeva Vault and can thereby be used for management of document workflows. Once a document is approved, it can be pushed into the Vault PromoMats document repository, which enables automated distribution to internal and external stakeholders.

**Knowledge Manager**

Knowledge Manager is a document repository

for published copies of publications that can be integrated with PMSolution. It can be used to search for publications and distribute them to internal and external stakeholders. Supporting information for users, such as documents supporting the rationale and key messages for the publication, can be added. Content can be searched based on tagged metadata that are manually entered.

**Conclusions**

Medical writers supporting scientific publications can enhance their productivity by using a comprehensive software solution that dovetails all aspects of publication management, from inception of a publication plan to final dissemination. Using a standardised software solution can assure a consistent process, reduce time spent managing the tasks in executing a publication plan, and ensure compliance with industry standards, transparency requirements, and standard operating procedures.

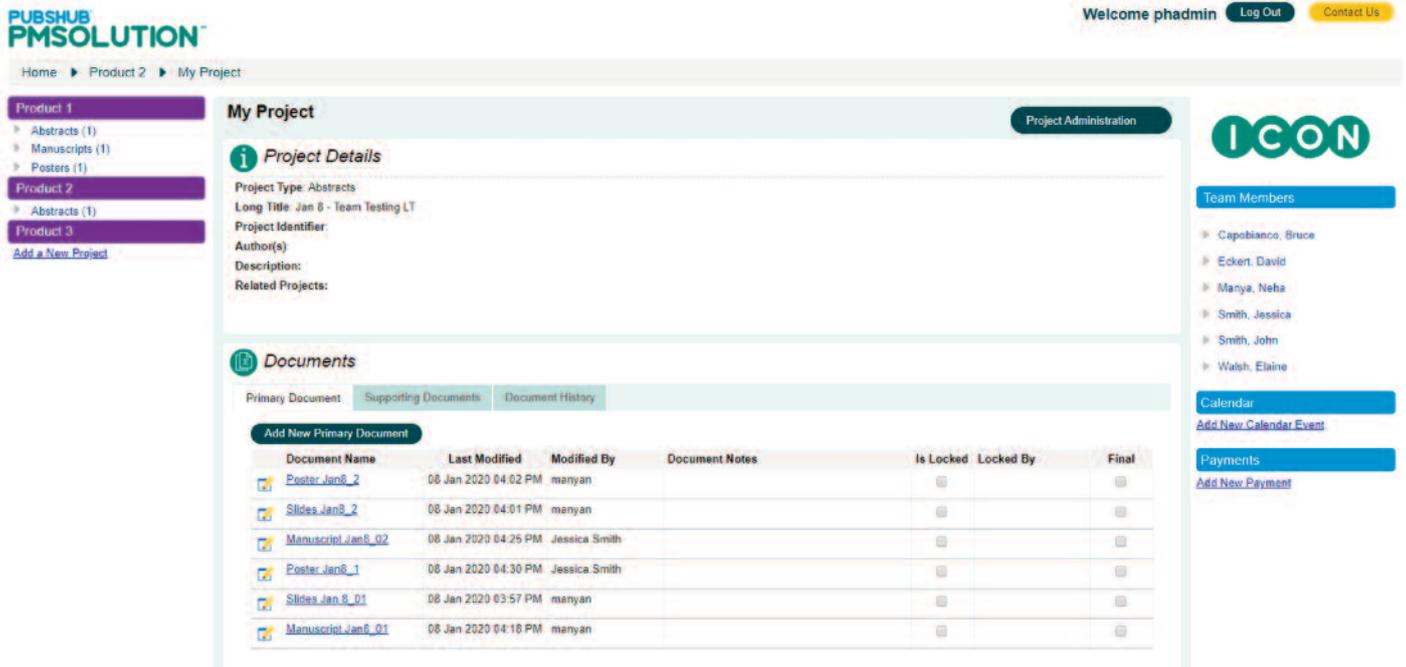


Figure 8. My Project dashboard page: PubsHub

From the Primary Document tab in PubsHub, project or product managers can access all publications in development. Revisions to publications can be uploaded into PubsHub from this page. From the Supporting Documents tab, users can upload sources used in review or quality control, and from the Document History tab, they can view versions and audit revisions.

While PubSTRAT, Datavision, and PubsHub include databases of journal and congress metrics to assist in publication planning, PubSTRAT and Datavision also include robust publication planning software packages with features that allow stakeholders to design, modify, and approve a publication plan. PubSTRAT and Datavision also include features to assist in executing the publication plan, including templates for invitation emails to authors, automated author eligibility checks, assignment of medical writing resources, and modifiable timeline templates. Datavision's integration with clinical trial management software allows for real-time updates in the publication management plan when study timelines change. Finally, Datavision's detailed dashboards allow managers to monitor the execution of the publication plan.

PubSTRAT, Datavision, and PubsHub support document review and approval, and all support simultaneous collaborative review rather than sequential review. They all include document repositories for published scientific communications that integrate with the Veeva Vault document management system. To further streamline the publication management, future

iterations of publication management software should include integration with journal submission platforms.

### Disclaimers

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

### Conflicts of interest

The author declares no conflicts of interest.

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**Don't miss!**

## The December 2020 edition



### **Writing for patients**

This issue will feature articles from some of the key opinion leaders in the area of writing for patients. We will cover aspects such as the current state of information given to patients and how we can do this better, the role of the medical writer with patient associations, the patient voice in research publications and writing up patient-reported outcomes, writing for the internet, and how patient needs are being incorporated into traditional medical communications.

**Guest Editors:**

**Lisa Chamberlain James and Amy Whereat**

# Regulatory Matters

## Immuno-oncology adaptive design studies

### Background for immuno-oncology studies

Accumulated research of more than a century has led to our current expansive understanding of the vertebrate immune system as a complex, multi-functional, evolutionary unit: a diverse, powerful, and adaptable network of cells and pathways that provides constant monitoring of the body to provide host defence against infection and inflammation.

Although an appreciation of the role of the immune system to prevent the development and/or progression of cancer is perceived to be more recent, the beginnings of cancer immunotherapy under different names may be traced back as far as antiquity. And several discoveries over the past 50 years in the field of immunology, such as, in 1967, the discovery of the existence of T cells and their crucial role in immunity, have brought the clinical world to the current state of research involving cancer immunotherapy that we know today.

Currently, research oncologists have come

to recognise that avoidance of immune destruction or suppression of natural anti-tumour immune responses are two of the escape mechanisms that allow cancer cells to grow, and both are widely accepted as emerging hallmarks of tumour resistance to anti-cancer treatment. Turning on the body's own immune system with biologic agents, including monoclonal antibodies and receptor agonists/antagonists, to combat cancer whilst dismantling key immune escape mechanisms (both part of so-called immuno-oncology therapy) represents a transformational approach to cancer care with a potential for long-term sustained efficacy.

### Adaptive design for immuno-oncology studies

Emerging clinical evidence supporting the development of new agents with diverse mechanisms of action has also raised the possibility that combination therapies could potentially lead to both greater depth of

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response and prolonged survival. Such combinations could also aid in combating the avoidance/suppression “strategies” employed by various neoplasms. Proof of principle has been established with the combination of anti-PD-1 and anti-CTLA4 in patients with advanced melanoma.<sup>1</sup> At the same time, the large number of potential therapeutic combinations has created an issue of practicality for industry, health authorities, and clinical investigators who all share the same goal of understanding which agents bring the greatest value to patients. Thus, there is a need for a clinical trial framework that facilitates a robust assessment of novel combinations across a broad range of patient populations within any given tumour type, and which



allows for the evaluation of combinations relative to one another.

One strategy for such efficient, expeditious, and rigorous evaluation of combination therapies has been the implementation of a complex clinical trial design, which has the defining feature of separate parts that could, in effect, be perceived as individual clinical trials, but are in fact elements of a single protocol. This approach is characterised by extensive adaptations, such as planned additions of new investigational medicinal products or new target populations. One such specific design is the master/sub-protocol clinical trial concept.<sup>2</sup> Master protocols, which apply to all combination treatments selected for evaluation under a tumour-specific study, define:

- The overall study plan
- The background and rationale
- The study design and duration
- Inclusion and exclusion criteria
- Time and events, including all procedures, labs, pharmacokinetics (PK), and pharmacodynamics (PD) that are not treatment specific
- The statistical plan

Additional treatment combinations can then be introduced into the study via sub-protocols that are appended to the master protocol for that study and include information appropriate to the specific treatment combinations and/or contemporaneous controls being added.

An important regulatory component of this design, and one that sponsor global regulatory functions may consider carefully, is that each study (including both master and sub-protocols) can be identified by single EudraCT and IND numbers, with all elements being linked by a single research hypothesis. Each sub-protocol is then submitted as a substantial amendment for separate regulatory and ethics committee review prior to implementation. The sub-protocols detail the specific study treatments and contain:

- Background – scientific rationale to support evaluation of additional combinations based on preclinical and clinical data
- Preclinical toxicology on single agents
- Clinical safety package for new agents
  - Monotherapy safety information
  - Combination safety data on at least six participants to support the protocol-specified dose; although safety data may be from a different patient population and/or tumour type
- Drug dose and administration

- Adverse events and dosing modifications
- Treatments and evaluations that include treatment-specific procedures, including PK (not found in the master protocol)

## Reporting challenges for adaptive design studies

For health authorities across the world, data transparency and safety are considered hallmarks of modern ethical clinical research. For EU/EEA and US FDA, consistent with these goals, the summary clinical study reports for Phase II-IV and paediatric Phase I trials are provided not only to competent authorities, but are also published on the public EU and FDA Clinical Trials Register within one year of the end of the trial (last-patient-last-visit [LPLV]), and even earlier for paediatric clinical trials (6 months).<sup>3,4</sup>

Complex clinical trials are most often early exploratory trials in relatively few participants and, therefore, the limited availability of safety data make transparency even more of a regulatory/clinical obligation. One challenge and potential obstacle in regard to data transparency for studies with a master/sub-protocol design may be that, when all sub-protocols within the master protocol design are registered with the same EudraCT and IND numbers as the master, information from each completed sub-protocol will become available only after the end of the entire trial. This circumstance limits the technical obligation for regulatory reporting of multiple treatment arms (sub-protocols) to one year post LPLV, thus reducing the documentation burden, but increases the need to find robust and ethical reporting strategies.

For complex clinical designs registered as one trial, for timely and transparent reporting of key information, sponsors are strongly advised to engage health authorities to propose periodic safety/status reports that provide a summary of the current study status, including:

- How many participants have been enrolled, randomised, and treated
- Which arms have been closed or newly opened
- Proposed plans for the next periodic interval, including known amendments or upcoming sub-protocol initiations
- Presentation of overall safety parameters (adverse events, serious adverse events, discontinuations, deaths, etc.)
- An assessment of the overall benefit/risk of the trial should be provided for each amendment of a new sub-protocol

addressing how all the risks will be mitigated

Sponsors are also strongly advised to include data from closed sub-protocols in the appropriate investigator's brochure.

The pharmaceutical industry has firmly embraced the current era of combinatorial clinical trial design, with the intention of quickly, accurately, and safely conducting investigations to increase the options for patients with cancer. This new era offers great promise for additional progress in the battle against neoplastic diseases in their many forms. Communication within sponsor regulatory and clinical organisations, in addition to robust interactions between such organisations and the relevant health authorities, are critical to ensure the realisation of such potential.

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# News from the EMA

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*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)*



## EMA recommendations on testing for the enzyme dihydropyrimidine dehydrogenase prior to treatment with fluorouracil, capecitabine, tegafur, and flucytosine

**April 30, 2020** – EMA has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur. Patients who completely lack DPD must not be given any fluorouracil medicines. For patients with partial deficiency, the doctor may consider starting cancer treatment at lower doses than normal or stopping flucytosine treatment, if severe side effects occur. These recommendations do not apply to fluorouracil medicines used on the skin for conditions such as actinic keratosis and warts, as only very low levels of the medicine are absorbed through the skin.

A significant proportion of the general population has a deficiency of DPD, which is needed to break down fluorouracil and the related medicines capecitabine, tegafur and flucytosine. As a result, following treatment with these medicines, fluorouracil can build up in their blood, leading to severe and life-threatening side effects such as neutropenia (low levels of neutrophils, a type of white blood cells needed to

fight infection), neurotoxicity (damage to the nervous system), severe diarrhoea and stomatitis (inflammation of the lining of the mouth).

Patients can be tested for DPD deficiency by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations in the gene for DPD. Relevant clinical guidelines should be taken into consideration. Therapeutic drug monitoring of fluorouracil may improve clinical outcomes in patients receiving continuous fluorouracil infusions.

Fluorouracil given by injection or infusion and its prodrug medicines (capecitabine and tegafur) are used to treat various cancers. They work by interfering with enzymes involved in making new DNA, thereby blocking the growth of cancer cells. Fluorouracil applied to the skin is used for various skin conditions such as actinic keratosis and dermal warts.

Flucytosine is related to fluorouracil and is used to treat severe yeast and fungal infections, including some forms of meningitis (inflammation of the membranes that surround the brain and spinal cord). As treatment for severe fungal infections should not be delayed, the pre-

treatment testing for DPD deficiency (which may take up to one week) is not required in these cases. Nevertheless, treatment with flucytosine is contraindicated in patients with known complete DPD deficiency due to the risk of life-threatening toxicity. In case of drug toxicity, consideration should be given to stopping treatment with flucytosine. Determination of DPD activity may be considered where drug toxicity is confirmed or suspected.

The review concerned fluorouracil medicines given by injection or applied to the skin as well as medicines containing capecitabine and tegafur taken by mouth (so-called fluorouracil prodrugs), which are converted to fluorouracil in the body. It also includes the antifungal medicine flucytosine which is given by injection or by mouth and some of which is converted into fluorouracil in the body. The review was initiated March 2019 at the request of the French Medicines Agency (ANSM). The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

## EMA commissions independent research to prepare for real world monitoring of COVID-19 vaccines

**May 27, 2020** – EMA is engaging early with researchers to ensure that a European infrastructure will be in place to effectively monitor COVID-19 vaccines in the real world, once these are authorised in the European Union. The Agency has signed a contract with Utrecht University as coordinator of the EU Pharmacoepidemiology and Pharmacovigilance Research Network, a public-academic partnership of 22 European research centres, to conduct preparatory research into data sources and methods that can be used to monitor the safety, effectiveness and coverage of COVID-19 vaccines in clinical practice. The ACCESS (vACCine Covid-19 monitoring readinESS) project will be led by the University Medical Center Utrecht (UMCU) and Utrecht University.

To authorise any COVID-19 vaccine, EMA will need to have strong evidence from clinical trials on the safety, efficacy and the quality of this vaccine. Once on the market, approved vaccines will be monitored closely, by the



Agency and its PRAC, through planned and routine pharmacovigilance activities, including the spontaneous reporting of suspected side effects reported by patients and healthcare professionals through Eudravigilance, the European database of suspected adverse reactions to medicines. The infrastructure put in place by Utrecht University will provide additional information from clinical practice to complement data collected pre-authorisation through clinical trials and post-authorisation through spontaneous reporting.

The researchers will identify a Europe-wide network of data sources (including health insurance records, GP and hospital health

records) and examine their utility in monitoring the coverage, safety and effectiveness of COVID-19 vaccines. The commissioned research will also identify possible adverse events of special interest that might need extra consideration in the monitoring of COVID-19 vaccines.

The research commissioned by EMA will be complemented by international collaboration on COVID-19 vaccine monitoring as agreed by the International Coalition of Medicines Regulatory Authorities (ICMRA) at its meeting on 19 May 2020. First deliverables of the commissioned research are planned for August 2020 with a final delivery by the end of the year.

## European regulators make recommendations drawing on lessons learnt from presence of nitrosamines in sartan medicines

**June 23, 2020** – The European medicines regulatory network has issued recommendations on impurities in medicines following the conclusion of an exercise to draw on lessons learnt from the presence of nitrosamines in a class of blood pressure medicines known as sartans. Although the exercise focused on nitrosamines in sartans, the recommendations will help reduce the risk of impurities being present in other medicines and ensure that regulators are better

prepared to manage cases of unexpected impurities in the future.

The recommendations aim to clarify the roles and responsibilities of companies involved in the manufacture of medicines and to amend guidance on controlling impurities and good manufacturing practice. The recommendations also cover the management of impurities once detected, communication with patients and healthcare professionals, and international cooperation. The

full recommendations are on EMA's website.

Nitrosamines are classified as probable human carcinogens (substances that could cause cancer) based on animal studies. The network noted that nitrosamines were not previously recognised as potential impurities in sartan medicines, and these recommendations will help both regulators and companies better prevent and mitigate the risks of these and other impurities in the future.

Regulators in the EU first became aware that nitrosamines were present in some sartan medicines in mid-2018. The discovery led to swift regulatory action, including the recall of medicines and measures to stop the use of active substances from certain manufacturers. A subsequent EU review, which concluded in April 2019, established the sources of nitrosamines and set out new manufacturing requirements for sartans. In September 2019, EMA launched an Article 5(3) procedure to provide additional guidance to companies that make and market medicines in the EU.



## First COVID-19 treatment recommended for EU authorisation

**June 25, 2020** – EMA’s human medicines committee (CHMP) has recommended granting a conditional marketing authorisation to Veklury (remdesivir) for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen.

Remdesivir is the first medicine against COVID-19 to be recommended for authorisation in the EU. Data on remdesivir were assessed in an exceptionally short timeframe through a rolling review procedure, an approach used by EMA during public health emergencies to assess data as they become available. From 30 April 2020, the CHMP began assessing data on quality and manufacturing, non-clinical data, preliminary clinical data and supporting safety data from compassionate use programmes, well in advance of the submission of the marketing authorisation application on 5 June.

The assessment of the dossier has now concluded with today’s recommendation, which is mainly based on data from study NIAID-ACTT-1, sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), plus supporting data from other studies on remdesivir.

Study NIAID-ACTT-1 evaluated the effectiveness of a planned 10-day course of remdesivir in over 1,000 hospitalised patients with COVID-19. Remdesivir was compared with placebo (a dummy treatment) and the main measure of effectiveness was patients’ time to recovery (defined as no longer being hospitalised and/or requiring home oxygen or being hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care).

Overall, the study showed that patients

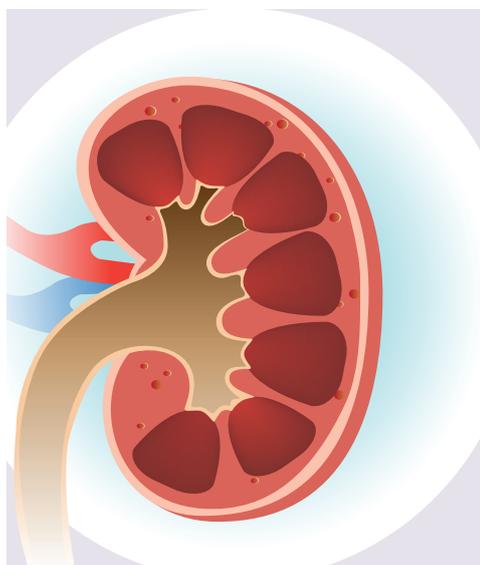
treated with remdesivir recovered after about 11 days, compared with 15 days for patients given placebo. This effect was not observed in patients with mild to moderate disease: time to recovery was 5 days for both the remdesivir group and the placebo group. For patients with severe disease, who constituted approximately 90% of the study population, time to recovery was 12 days in the remdesivir group and 18 days in the placebo group. However, no difference was seen in time to recovery in patients who started remdesivir when they were already on mechanical ventilation or ECMO (extracorporeal membrane oxygenation). Data on the proportion of patients who died up to 28 days after starting treatment are currently being collected for final analysis.

Taking into consideration the available data, the Agency considered that the balance of benefits and risks had been shown to be positive in patients with pneumonia requiring supplemental oxygen; i.e., the patients with severe disease. Remdesivir is given by infusion (drip)

into a vein and its use is limited to healthcare facilities in which patients can be monitored closely; liver and kidney function should be monitored before and during treatment, as appropriate.

In order to better characterise the effectiveness and safety of remdesivir, the company will have to submit the final reports of the remdesivir studies to the Agency by December 2020, and further data on the quality of the medicine, as well as the final data on mortality, by August 2020.

During the assessment of remdesivir, the CHMP had the support of experts from the COVID-19 EMA pandemic task force (COVID-ETF), which was established to bring together the most relevant expertise from the European medicines regulatory network to assist Member States and the European Commission in dealing with the development, authorisation and safety monitoring of medicines and vaccines against COVID-19.



## New treatment to enable kidney transplant in highly sensitised patients

**June 26, 2020** – EMA has recommended granting a conditional marketing authorisation in the European Union for Idefix (imlifidase), the first treatment for adult patients waiting for a kidney transplant, who are highly sensitised against tissue from the donor and who have a positive crossmatch test against an available kidney from a deceased donor. Idefix should be used complementary to existing allocation programmes for patients with a very low chance of finding a matching kidney despite such programmes.

When a kidney from a deceased donor is

offered for transplant, crossmatch tests are performed against all patients on the waiting list. The test checks whether a patient has specific antibodies against the potential donor.

Highly sensitised patients have exceptionally high antibody levels that react to the donor’s tissue which shows up as a positive crossmatch test, making it more likely that the body will reject the donor organ. Patients with this result are therefore not eligible for transplant, and the available kidney is typically offered to other patients on the waiting list. There is an unmet medical need to desensitise these patients and



## COVID-19: EMA sets up infrastructure for real world monitoring of treatments and vaccines

**July 24, 2020** – EMA has now set up an infrastructure to support the monitoring of the efficacy and safety of COVID-19 treatments and vaccines when used in day-to-day clinical practice. This is underpinned by three contracts for observational research that EMA has signed with academic and private partners over recent months, to be ready to effectively monitor vaccines in the real world as soon as they are authorised and support the safe and effective use of COVID-19 vaccines and medicines.

The latest contract was finalised in mid-July with Utrecht University and the UMCU as coordinators of the CONSIGN project ('COVID-19 infectiOn aNd medicineS In preGNancy'). This project will collect data on the impact of COVID-19 in pregnancy in order to guide decision-making about vaccine indications, vaccination policies and treatment options for COVID-19 in pregnant women. CONSIGN will analyse existing data sources (e.g. electronic health records, hospital data) and cohorts of pregnant women to provide information on the effect of infection and its treatments in different trimesters of pregnancy and on neonates. The project will be carried out in collaboration with the ConcePTION consortium, which was established under the EU's Innovative Medicines Initiative, the COVI-

PREG project and the International Network of Obstetric Survey Systems network.

In June, EMA contracted the company IQVIA with a project to build a framework for the conduct of multicentre cohort studies on the use of medicines in COVID-19 patients. This project will include the identification of large national cohorts of COVID-19 patients and appropriate comparator groups, the development of a study protocol template for multinational studies as well as the establishment of a collaborative framework for researchers. The project will be carried out in collaboration with the European Health Data & Evidence Network consortium, which was established under the Innovative Medicines Initiative and includes the Erasmus Medical Centre in Rotterdam and the University of Oxford as project lead and research coordinator, respectively.

In May, EMA commissioned the ACCESS project ('vACCine Covid-19 monitoring readinESS') for preparatory research into data sources and methods that can be used to monitor the safety, effectiveness and coverage of COVID-19 vaccines in clinical practice, once authorised.

Observational research is an important pillar in the post-marketing surveillance of COVID-19 treatments and vaccines and EMA has called for transparency for protocols and results, as well as

collaboration between researchers, to ensure high-quality, powerful studies. To facilitate this, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), which is coordinated by EMA, has set up a dedicated COVID-19 response group. EMA and ENCePP are encouraging researchers to register their pharmacoepidemiological studies (and make study protocols and reports public) in the European Union electronic register of post-authorisation studies (EU PAS Register), to ensure transparency on the various research efforts.

EMA is also fostering international collaboration on observational research through the ICMRA, with the agreement to step up co-operation in three areas: pregnancy research, building international clinical cohorts of COVID-19 patients and preparing a strong infrastructure for monitoring the safety and effectiveness of vaccines.

The outcome of the various projects conducted on observational research will be fed into the work of EMA's COVID-19 EMA pandemic Task Force (COVID-ETF) and EMA's scientific committees, to ensure that this evidence is translated into scientific opinions on the optimal use of the medicines and vaccines concerned.

convert a positive crossmatch into negative for them to become eligible for kidney transplantation.

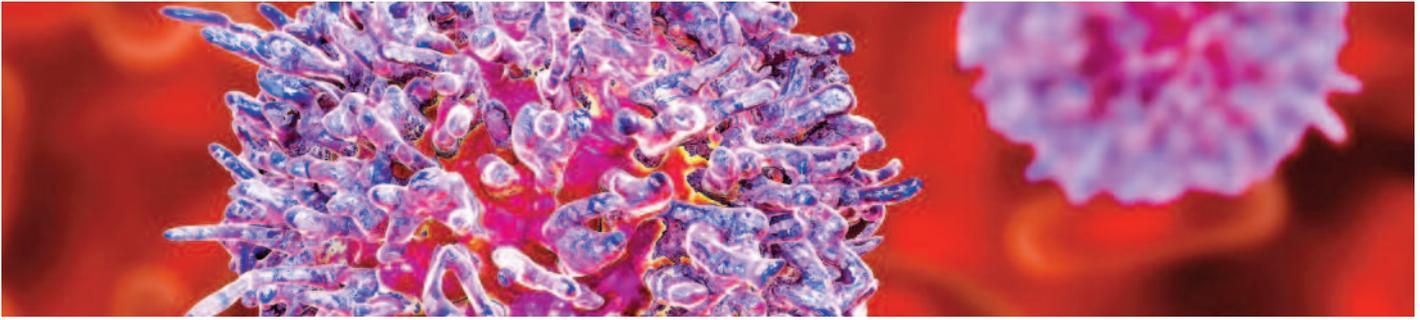
Idefix is made of an enzyme derived from the bacterium *Streptococcus pyogenes*, which breaks down antibodies called Immunoglobulins G (IgG). IgG is produced by the patient against the transplanted organ. By breaking down IgG, the medicine is expected to prevent the patient's immune system from attacking the newly transplanted organ, thereby reducing the risk that the organ will be rejected.

The efficacy and safety of Idefix as a pre-transplant treatment to reduce donor specific IgG and enable highly sensitised transplant candidates to be eligible for kidney transplantation, was

studied in three open label, single arm, six-month clinical trials. In these studies, 46 sensitised patients were transplanted. All patients who were crossmatch positive when included in the study were converted to negative within 24 hours after treatment with imlifidase. The studies showed excellent results on kidney function and graft survival after six months. The most common adverse reactions reported with this treatment were infections, such as pneumonia, urinary tract infection and sepsis and infusion-related reactions. The effect of Idefix is temporary, and therefore does not preclude the need for standard immune suppression in kidney transplant patients.

Idefix (Hansa Biopharma AB, Sweden) was 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 the potential to address patients' unmet medical needs. Idefix is recommended for a conditional approval. This type of approval allows the Agency to recommend a medicine for marketing authorisation with less complete data than normally expected, in cases where the benefit of a medicine's immediate availability to patients outweighs the risk inherent in the fact that not all the data are yet available. The company must now submit additional efficacy and safety data based on one observational follow-up study and one post-approval efficacy study.



## First antibody-drug conjugate for multiple myeloma patients with limited treatment options

**1 July 24, 2020** – EMA's CHMP has recommended granting a conditional marketing authorisation in the European Union for Blenrep (belantamab mafodotin) to treat adult patients with relapsed and refractory multiple myeloma who no longer respond to treatment with an immunomodulatory agent, a proteasome inhibitor and a CD-38 monoclonal antibody.

Multiple myeloma is a cancer of a type of white blood cell called plasma cells that is responsible for about 2% of all cancer deaths. Normal plasma cells are found in the bone marrow and are an important part of the immune system. Plasma cells make the antibodies that enable the body to recognise and attack germs such as viruses or bacteria. They originate from B-cell lymphocytes and form when B-cells respond to an infection. 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.

A range of new medicines for the treatment of multiple myeloma have been developed and approved in recent years, leading to a steady overall improvement in survival of patients. However, for patients who have already been treated with three major classes of drugs (immunomodulatory agents, proteasome inhibitors

and monoclonal antibodies) and no longer respond to these drugs, the outlook is still bleak. There is an unmet medical need for new treatments that improve survival of these patients beyond the currently observed three months or less.

Blenrep has a new mechanism of action that targets B-cell maturation antigen (BCMA), a protein that is present on the surface of virtually all multiple myeloma cells. BCMA is absent from normal B-cells, making it an ideal drug target. Structurally, Blenrep is an antibody-drug conjugate that combines a monoclonal antibody with maleimidocaproyl monomethyl auristatin F (mcMMAF), which is a cytotoxic agent. The medicine binds to BCMA on myeloma cell surfaces and once inside the myeloma cell, the cytotoxic agent is released leading to apoptosis, the 'programmed' death of the cancerous plasma cells.

The main study on which the CHMP's recommendation for a conditional marketing authorisation is based was a phase 2, open label, randomised, two-arm study. The study investigated the efficacy and safety of two doses of belantamab mafodotin in multiple myeloma patients whose disease was still active after three or more lines of therapy and who no longer responded to treatment with immunomo-

dulatory drugs and proteasome inhibitors and who did not respond to treatment with an anti-CD38 monoclonal antibody. The most common side effects found in participants in clinical trials with Blenrep were keratopathy (a disease affecting the cornea, the transparent layer in front of the eye that covers the pupil and iris) and thrombocytopenia (a condition that causes low blood platelet counts, which can lead to bleeding and bruising).

In order to better characterise the effectiveness and safety of the medicine, the company will have to submit the results of a randomised confirmatory (phase 3) trial comparing Blenrep with pomalidomide plus low-dose dexamethasone, which is a standard treatment option for relapsed and refractory multiple myeloma. The company is also required to submit the final results of the pivotal phase 2 study.

Blenrep (from GlaxoSmithKline Limited) was accepted in EMA's PRIME scheme and has benefited from the extra support offered by the Agency. Blenrep was designated as an orphan medicinal product on 16 October 2017. Following this positive CHMP opinion, the Committee for Orphan Medicinal Products will assess whether the orphan designation should be maintained.

Save the date:  
**EMWA Symposium**

**RESEARCH  
INTEGRITY**

<https://www.emwa.org/news/emwa-symposium-6th-november>



**6th November 2020**



## Editorial

After the cancellation of EMWA's Spring Conference this year, EMWA's Medical Device Special Interest Group stepped up to ensure that members did not miss out on the Expert Seminar Series (ESS) by organising a virtual version of the event. Cherry Malonzo

Marty provides a summary of the virtual ESS where medical device experts weighed in on drug-device combination products and an update on the new Eudamed database. In other news, preparations for the Medical Device Regulation continue even with implementation postponed to May 2021. Kerstin

Römermann and Wiebke Theilmann describe two new guidance documents for post-marketing clinical follow-up plan and report templates released earlier this year by the Medical Device Coordination Group that will guide you in preparing these new documents.

**Kelly**

## Virtual Expert Seminar Series

The first ever virtual EMWA Expert Seminar Series on Medical Devices was held on June 9, 2020. Attended by 39 participants, the majority having less than 5 years of professional experience in the medical device industry, the session was received positively with the new virtual format. The two talks in this series focused on drug-device combinations (DDCs) and the European Database on Medical Devices (Eudamed), two of the many open concerns surrounding the new Medical Device Regulations (MDR),<sup>1</sup> and concluded with a panel discussion.

### Drug-device combination regulation including Article 117

The first presentation by Jonathan Sutch from BSI UK focused on DDC products classified under Rule 14 and Rule 21 of the MDR and products that fall under Article 117. Beginning with regulatory definitions differentiating medical devices under the MDR and medicinal products under the Directives 2001/83/EC,<sup>2</sup> the presentation continued by explaining the concept of the primary Mode of Action (MOA) that will determine the applicable regulatory pathways for these types of products.

Rule 21 refers to devices containing substances (e.g., paraffin dress) which need to comply to Directive 2001/83/EC for

medicinal products.

Rule 14 on the other hand, refers to "medical devices with ancillary medicinal substances", in which the medical device acts as the primary MOA of the combination (e.g., drug-eluting stent), requiring compliance to the MDR. Though this type of product is sometimes referred to as "Device-Drug Combination" (also DDC), this is an informal name and should not be confused with integral DDCs falling under Article 117.

Article 117 of the MDR is an amendment to Directive 2001/83/EC, which applies to so-called integral DDCs such as inhalers or pre-filled syringes. Under this amendment, such products will now require either CE Marking on the device component or a Notified Body

(NB) Opinion (NBOP) to be included in the Market Authorisation Application of the medicinal product (Figure 1).<sup>3</sup> With the requirement of an NBOP, the medical device component of integral DDCs must conform to the relevant General Safety and Performance Requirements of Annex I of the MDR as justified by the device's intended purpose.

Medical writers contributing to the pre-market applications of combination products falling under Rule 14, Rule 21, or Article 117 will have to document according to the EU MDR as well as the medicinal product Directives 2001/83/EC, keeping in mind that the reviewers as well as the requirements are different for each. Though this may be a challenge for medical writers accustomed to writing for only one sector and not the other, this would also be an opportunity to learn the regulatory language necessary to fulfil the requirements of such combination product submissions.

### The new Eudamed under the MDR

The second talk was presented by Richard Houlihan, the technical IT manager for



## Regulatory Path

Principal Mode of Action (PMOA)  
Informs Regulatory Path

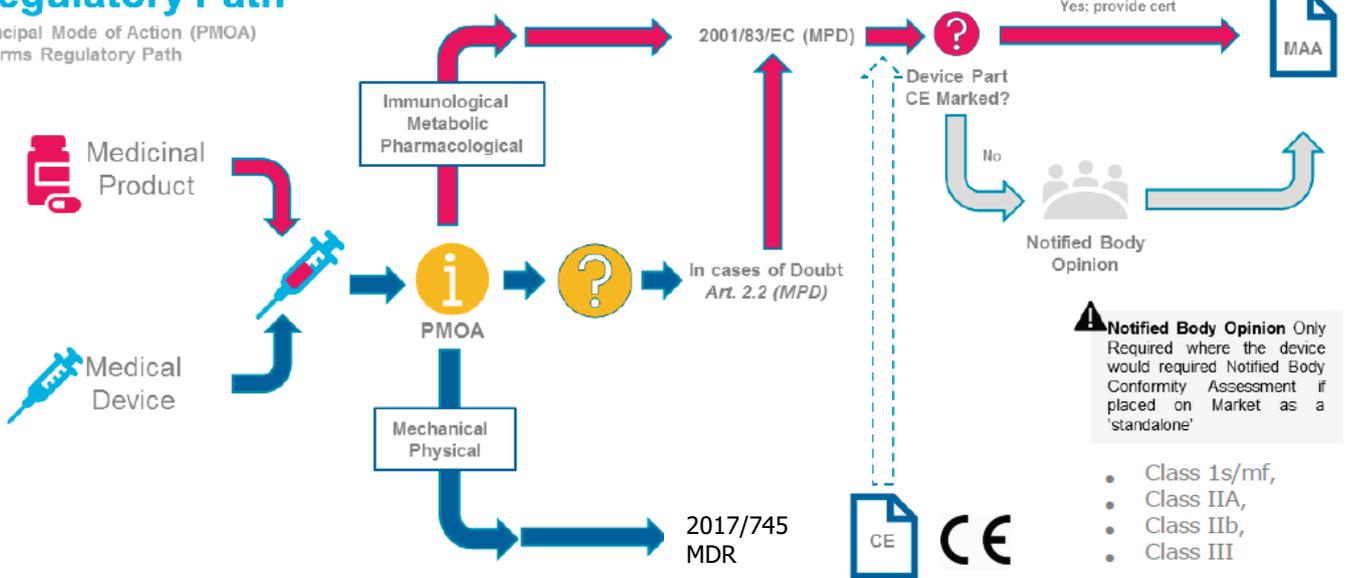


Figure 1. Future process (from May 26, 2021) for drug-device combinations under the Medical Device Regulation. Reprinted with permission from BSI UK.

Eudamed. This new database is now scheduled to go live in May 2022, when the new MDR and IVDR are already in place. The delay from the initial target date of May 2020 was announced earlier this year, citing the need for more time to ensure that the platform was fully

functional before launch. The presentation covered the scope of the new Eudamed, an update of the Eudamed2 that is currently only accessible to competent authorities and the European Commission. Eudamed, in comparison, is being built to be accessible to

all stakeholders, including the public, as a multi-purpose registration, collaboration, notification, and dissemination system.

With the large scope and six main modules that no other medical registration system implements to date, the challenges of develop-



Figure 2. Timeline of Eudamed module releases. Reprinted with permission from Eudamed Ltd.

ing and implementing the interoperable system are multifaceted. Namely, the decisions of the Medical Device Coordination Group (MDCG) to Eudamed were referenced,<sup>4</sup> including decisions on legacy devices and nomenclature to be implemented in the new system. Emphasis was made on the technicalities of the new Unique Identification Number (UDI) that will be implemented with the new EU MDR, as well as the need for all stakeholders to review relevant guidance documents, in order to understand the functionality and requirements for uploading data into the database.

Figure 2 shows the Eudamed timeline with a staggered release of the different modules until the database is fully functional in 2022.<sup>5</sup> Though the MDR application date has been postponed 1 year, Eudamed still intends to release the first module at the end of 2020 and latest by May 2021 in time for the new MDR application date. The presentation emphasised the extensive amount of preparation that will be required for the large data submissions into the Eudamed modules. Though the specifics of the modules cannot be publicly disclosed yet, early preparation could not be overstated in order to collate all the Eudamed data in time for submissions when the modules go live. From web-based forms to bulk uploads and machine-to-machine inputs, preparation and understanding of the requirements is key to

streamline the efforts of reporting. For medical writers, the potential of the EUDAMED system will not be optimised if data and documents do not fulfil the requirements in time for digital submissions.

### Expert panel Q & A

The ESS was concluded by panel discussions where the experts were joined by Jane Edwards from BSI and Gillian Pritchard from Sylexis. The presentations had shed some light on the fundamental concepts of DDCs and the importance of preparing for Eudamed submissions in time for the MDR application date. However, it is also apparent that there are still ongoing developments. Even a survey poll conducted during the ESS returned unsurprising results; the participants believed the MDR delay of a year was appropriate. Though the ongoing COVID-19 pandemic has led to the postponement of MDR implementation, giving stakeholders in industry more time to prepare for the transition, many questions remain regarding MDR-readiness. Until May 2021, we may expect demand for more sessions like these being conducted across industry to aid in the crucial preparations of all stakeholders for the inevitable transition.

### References

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## Post-market clinical follow-up plans and evaluation reports

In April 2020, the Medical Device Coordination Group (MDCG) endorsed post-market clinical follow-up (PMCF) plan and PMCF evaluation report templates as a guidance for manufacturers to ensure compliance with the relevant requirements. Here we aim to provide an overview of the contents of the MDCG template documents.

As PMCF plans and reports are reinforced under the Medical Device Regulation (MDR), uncertainties exist regarding which information has to be documented and how. Even though Annex XIV Part B of the MDR<sup>1</sup> provides the minimum requirements for a PMCF plan, the description is rather short and lacks detailed information. With the purpose to guide manufacturers in complying with the requirements of the MDR, the MDCG created

a template PMCF plan and PMCF evaluation report with detailed instructions on format and content. The MDCG template documents are not European Commission documents and not legally binding. They were designed to simplify the work of both, the manufacturer in complying with all relevant standards and the notified bodies or competent authorities in data extraction. Manufacturers who have already prepared their own PMFC plan templates might need to update them in order to capture any missing elements from the MDCG guidelines.

The PMCF plan and the PMCF evaluation report are similar in content and section structure. The templates are structured into seven sections (Table 1). Both documents shall be stand-alone documents and therefore,



**Table 1. Sections of the MDCG PMCF plan and PMCF evaluation report template documents from MDCG 2020-7 and MDCG 2020-8**

Template section heading		
Section	PMCF plan template	PMCF evaluation report template
A	Manufacturer contact details	Manufacturer contact details
B	Medical Device description and specification	Medical Device description and specification
C	Activities related to PMCF: general and specific methods and procedures	Activities undertaken related to PMCF: results
D	Reference to the relevant parts of the technical documentation	Evaluation of clinical data relating to equivalent or similar devices
E	Evaluation of clinical data relating to equivalent or similar devices	Impact of the results on the technical documentation
F	Reference to any applicable common specification(s), harmonised standard(s) or applicable guidance document(s)	Reference to any common specification(s), harmonised standard(s) or guidance document(s) applied
G	Estimated date of the PMCF evaluation report	Conclusions

Source: MDCG 2020-7<sup>2</sup> and MDCG 2020-8.<sup>3</sup>

the manufacturer details as well as device description and specification need to be documented in the first two sections. The PMCF plan contains a definition of the specific objectives as well as general and specific methods and procedures that will be conducted in the post-market period. This could be a screening of scientific literature and other sources of clinical data, post-market studies (e.g., prospective case series, retrospective patient record reviews, nested registry studies), analysing data in registries, surveys from health care professionals or patients/users, or reviews of case reports which may reveal misuse or off-label use. The choice of methodology should be based on the level of risk associated with the device, e.g., literature screening might be a sufficient PMCF activity for low risk, non-implantable devices with sufficient clinical evidence. Each PMCF method and procedure is described in detail in specific subsections. Within these subsections, the manufacturer will provide:

- A definition where the need of conducting the PMCF activity is coming from
- A description of activity and if it is a general

or specific method/procedure

- A definition of the aim of the respective activity
- A description of the respective methods
- A rationale for the appropriateness of the chosen methods/procedures. This includes and is not limited to justifications for sample size, endpoints, comparators, study design or statistics
- A detailed and adequately justified time schedule for all planned PMCF activities

Furthermore, a PMCF plan must document the evaluation of the clinical data related to equivalent or similar devices as defined in the clinical evaluation plan. These data may be used to update state of the art information or identify relevant safety outcomes. Nevertheless, the device under evaluation itself should deliver the data to demonstrate continuing safety and performance.

In the penultimate section, the PMCF plan and the PMCF evaluation report shall reference to the relevant parts of the clinical evaluation report and to the risk management (referred to in Section 4 and Section 3 of

Annex I)<sup>1</sup> and to any relevant common specifications, harmonised standards, and relevant guidance on PMCF, if applicable. The results of the manufacturer initiated PMCF analyses are stated in the PMCF evaluation report document. The overall conclusion of the findings is provided and related to the aims of PMCF in the last section of the PMCF evaluation report. Moreover, the conclusion focusses on necessary implementations of corrective and preventive actions. The conclusion will also be part of the following clinical evaluation, the risk management file, and gives input into the next PMCF plan.

Still, several uncertainties exist regarding which and how PMCF information must be documented under the MDR. Thus, the MDCG templates provide a helpful tool to simplify and accelerate the work of manufacturers and notified bodies.

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1. European Commission. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE. [cited 2020 Jul 1]. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745>
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# Medical Communications and Writing for Patients

## Dear All

I'm writing this to you from lockdown. Some of us will be out of lockdown by the time you read this, and perhaps others of us will be back in! Either way, I pray that you and your families are all safe and healthy.

In this issue of *Medical Writing*, I'm delighted to present a piece from Dr Joana Fernandes, who discusses her early career as a science/medical news writer, writing articles for a non-scientific audience. Joana explains the importance of writing for this audience; the

importance of making sure that the articles are scientifically sound, accurate, and easy to follow, as a way to bring science and medicine closer to the public.

Joana is a medical writer at Scinopsis, UK. She obtained her PhD in Cellular and Molecular Biology from the University of Coimbra, Portugal, in 2014. She has over 8 years of experience in scientific research and has been working as a science/medical writer since 2016.

I hope that you enjoy Joana's insights into life as a medical news writer – perhaps it might

## SECTION EDITOR



**Lisa Chamberlain James**

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inspire you to become more involved in this expanding area of medical writing.

In the meantime, stay safe and sane in lockdown, and see you in the December issue!

**Bestest,  
Lisa**

## Sense and sensibility: Lessons from science/medical news writing

Immediately after I left the bench to pursue a medical writing career, I started working remotely for a US-based digital health news service. Its purpose was to share new scientific and pharmaceutical developments with the people who need it the most: patients and caregivers. Shortly after I started, I began appreciating the responsibility associated with that job. These readers frequently go online to find out more information about disease, for themselves or a loved one, and thus it was crucial

to guarantee that my writing was clear, accurate, and honest. In this article, I discuss a few things that I learned at that job and that may hopefully help others to write for non-scientific audiences.

### Switching audiences from peers to non-scientific readers

As part of that company, I wrote more than 20 articles a week, most of which covered the latest developments in research and treatment in chronic disease, including neurodegenerative,

oncologic, respiratory, muscular, metabolic, inflammatory, and autoimmune diseases. My job required that I read multiple research studies and interpret data from clinical trials, and then combine journalistic skills with my scientific knowledge to report medical news in an engaging way. I also spoke to doctors and scientists standing at the forefront of important research and, perhaps more importantly, I interviewed patients who, stricken with certain diseases, provided a true account of how they adapted to their condition, their frustrations and accomplishments, their experience of what it is like to manage their lives in the face of life-changing obstacles. For this reason, patient stories were particularly rewarding to write and publish, as they served as examples of persistence, strong will and a great desire to live, and certainly served as inspiration to everyone.

I look back at those times as a science/medical news writer fondly, it was a marvellous experience. I was mentored by experienced journalists who taught me how to prepare interviews and write articles that would keep readers engaged until the last paragraph. It was incredibly rewarding to play the part of a "science/medical news Hermes" who delivered valuable messages and first-hand news about what was being done to advance treatment and patient management. However, as old Peter Parker's uncle once said, with great power comes



great responsibility, and writing about disease and treatment for an audience that will eagerly consume such news is a big deal. Sometimes, we see journalists using flashy titles (“the cure for cancer is near”) or even utterly false news (“experts warn against vaccine that leads to autism”) to get their readers’ attention, to the detriment of the good old deontological code for journalism. This should never be the case for a medical journalist or science writer – quite the opposite. It is important to keep in mind that patients tend to go online to find more information about their disease, so it is our duty as both writers and scientists to provide them with trustworthy, accurate information.

But this was exactly where the trickiest part of my old job lay. How does a science/medical news writer prepare a piece that is both accurate, easy to follow, and interesting to read until the end? As scientists, we are used to discussing scientific facts with our peers; our background knowledge makes it tempting to resort to scientific jargon and specific language to guarantee the accuracy of what we are writing, not to mention the constant effort to avoid generalisations and the omission of important details which otherwise might result in misleading narratives. It is especially tricky when we need to report specific terms that are hard to put in simpler terms or even uncertainties or nuances that arise from results analysis and the supporting statistics of a given study. However, the use of specialised language is discouraged when you are writing for a non-scientific audience, as these readers will likely find it difficult to understand and even boring.

Fortunately, there are several tips that we can try to follow to make our job a bit easier when it comes to adapting our language to a non-scientific audience, such as those presented and discussed by Joselita Salita in her article “Writing for lay audiences: a challenge for scientists”.<sup>1</sup> To quote Salita, “lay communication is not just taking out jargon and replacing it with more understandable text but rather a complete ‘repackaging’ of the scientific message”. Indeed, the zest to being a science/medical news writer is to write pieces that are simultaneously informative and compelling to read. Replacing words is not enough to achieve this, the enthusiasm of reporting must still be there.

## Sorting the wheat from the chaff: Not all details matter

Back in those days, most of my weekly work was reading freshly published scientific research



papers and write a small article with the readers’ perspective in mind. After all, patients and caregivers are not interested in knowing the very same details that will excite a scientist. But this was not so obvious to a scientist freshly out of the lab. Indeed, a scientific article and a news article could not be more distinct, and this is reflected in the order in which the information is presented. While scientific articles follow the traditional pyramid structure that starts with background information, followed by discussion and conclusion, a science/medical news article follows the opposite order: it starts with the conclusion (the “lede”, as journalists call it, the main message), which is then followed by background information (context) and some details from the discussion, which can be interesting to the reader (depending on the story). The conclusion/lede is what captures the readers’ attention at the very first paragraph: it tells the readers what is new, why the article was written, what important message we wanted to share. We start with the why: why is this study important? Because something relevant was found and may even help scientists develop new therapeutic strategies, for example.

It is important to note that the title of the scientific paper will not necessarily make a good lede. Consider, for example, the scientific study titled “Loss of Frataxin Activates the Iron/

Sphingolipid/ PDK1/Mef2 Pathway in Mammals”. A lede that uses these words to introduce what our news article is about will certainly scare the readers away: it is too specific and too scientific. It is far more likely that readers will want to read our article if we start by saying that “a new study in mice identified the mechanism through which loss of frataxin, the protein missing in Friedreich’s ataxia, leads to the death of neurons”, and that this finding could be helpful in developing potential future treatments for this disease.

As we work our way from conclusion to background information, we leave out several details that may not be relevant for a non-scientific reader. In contrast to scientists, these readers will not care about whether a given study was published in *Nature* or *Science* or whether the authors used the latest state-of-the-art microscope technique or the correct statistical tests. While our experience as scientists makes it tempting to explain everything in

detail and leave little room for misleading conclusions, when writing for a non-scientific audience we need to select what is truly important for the reader: *Are these results trustworthy? Does this add anything to the research done in this disease? Will these results lead to the development of a new treatment, and if so, when? Can these results potentially help patients in any way?* In this context, sorting the wheat from the chaff consists of addressing these specific questions while preparing our articles and leaving out anything superfluous that may be distracting or confusing.

## Source material with a pinch of salt

As Jo Whelan once said, *true journalism involves doing background research into the context surrounding the finding being reported, seeking comments from independent experts, and highlighting the negative as well as the positive aspects.*<sup>2</sup>

Another important aspect about writing for a non-scientific audience is to analyse the source materials in a critical manner and avoid taking them at face value. When I was a science/medical news writer, I received all sorts of material to base my articles on, often newly published research studies. Naturally, these studies presented different levels of quality.

Well-designed studies were easy to follow from a scientific perspective, so my job was to ensure that the message was delivered with clarity and accuracy, without exaggerating or even forcing the impact of the results just because they



were scientifically sound or were published in a high-ranked journal. For example, a significant drug-induced reduction in tumour burden in mice may be good news, but we cannot extrapolate that to humans and say that a new cancer treatment has been found. As we know, there is a substantial amount of work to be done before we can say something like that, and writers need to make that very clear.

I also came across research studies whose quality or impact were a lot less strong and that I would have preferred to leave out, but the company I worked for had a daily need to cover any new material, so sometimes I had to write about these studies as well. These studies were sometimes published in non-peer-reviewed journals, or had no control group, or were case reports about a single patient. A well-trained scientist will read these studies with a pinch of salt (or several) and know that their design and results make it hard to draw strong scientific conclusions, let alone medical conclusions. Again, this must be part of the message in news articles. It is crucial to make it very clear to the reader that those results were obtained in studies with certain limitations and that results must be interpreted with caution. I believe it is the writers' job to highlight the context in which results were obtained and, more importantly, what is their true contribution and value to the research done in a given disease.

When reporting on new scientific/medical advances for a non-scientific audience, writers

should guarantee that certain tips are followed to ensure that the final piece is sound and clear. In her article *Medical journalism – a career move?*,<sup>3</sup> Jo Whelan recommended several useful guiding tips:

- We should never take press releases, corporate publications, or newspaper/magazine articles at face value – we must always use our scientific skills to critically analyse the source material. If we are writing about a topic outside of our main expertise, it may be helpful to look up other reading sources as well or speak to an expert;
- It is crucial to get the background on our story (background reading will definitely help understand the impact/importance of the material we have to cover for our article);
- Whenever possible, we should interview someone (for example, the authors of the study) for our article, ask searching questions or get an independent expert to comment;
- We must be aware of people's motivations, agendas, conflicting interests, and potential prejudices;
- We should never report statements as facts and should always use qualifying phrases like “according to Kuritech”, or “says Dr X” (I also used “the authors wrote in their study” when quoting directly from a research paper).

## Conclusion

Writing for non-scientific audiences is a very interesting job that teaches writers to adapt their

language and choose carefully what details are relevant to share. Patients and caregivers increasingly rely on digital material to find out more about disease, thus writers must consider the impact their writing has. It is not enough to write a compelling read, they must also be accurate and clear about the science they are reporting and use their skills to help readers understand what is true and relevant, and what is not.

## Disclaimer

The views expressed in the submitted article are the author's own and not an official position of Scinopsis Ltd or EMWA.

## Acknowledgements

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# Getting Your Foot in the Door

## Editorial

Once again, we have two incredible stories in this edition of GYFD. Priyanka shares with us her amazing story and the creative strategy she pursued to get a much needed industry job in corona times.

Equally amazing is Diana's journey from the

pharmacy counter to freelance medical writing, an inspiration to those who are thinking of shifting careers.

To both of you, welcome to the club and happy writing!

**Raquel Billiones**

## SECTION EDITOR



**Raquel Billiones**

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## If you don't ask, the answer is always no

Growing up in a small town in India, where women hardly work, my only dream was to get a job and be independent. So when I got a PhD position in Germany, it was far more than I had dreamt of. I loved being at the bench and planning and analysing my experiments. I also discovered a newfound love for hiking in the European countryside. But some years into PhD and the constant struggle of my PhD supervisor for a tenured position, made me realise that academia was not a viable career option for me.

I started looking for alternative career paths and reading job ads, which led me to Medical Writing. It seemed like an enticing career option as I always had a penchant for writing, be it writing diaries or letters to people. My PhD also exposed me to scientific writing in many forms and so I felt confident about transitioning to a medical writing career. But, of course, it is difficult to break out of the cocoon of academia, where you are surrounded by scientists with very linear academic paths, which omits much room for flirting with other career paths.

However, I was already aware of the power of networking from the job search of my husband. Just a casual browse in LinkedIn led me to a video where a guy talked about taking initiative and summarised with a powerful quotation: "If you don't ask, the answer is always no". This quotation helped me to break that cocoon, and I reached out to a few medical writers, asking for their advice. The response I got was amazing; these were people who were in the same boat once, so they tried to give the best possible direction they could.

Most medical writers encouraged me to

participate at the EMWA conference to gain more insights and take workshops to gain first-hand experience. I was a bit apprehensive at first, but once at the conference, I felt really welcomed as I met some of the most inspiring people with whom I connected instantly and remain connected. I attended a few workshops and seminars by leaders in medical writing. More importantly, I met my mentor Sarah Tilly of Azur Health Science, who played a huge role in my transition. I took a long-distance mentoring programme under her and learned the basics of regulatory writing.

I was already applying for some time with hardly any response. Although a PhD already equips you with most skills needed for an industry position, I realised that the companies are not so convinced and that they look for industry experience. So, in a desperate attempt to gain further industry experience, I took the initiative to contact Trilogy Writing and Consulting. Looking at my interest in medical writing, they agreed to take me on as an intern for 2 months. This stint gave me the experience I needed on actual regulatory documents and also a sneak-peak on how the medical writing industry worked.

After the internship, I started applying for industry positions, and this time I started getting a more positive response. I guess the companies saw that I had two industry experiences and they showed interest in my CV. Being in Germany, another key factor is learning the language, and it helped that I already had gained B2 level German skills. So I had two job interviews for regulatory affairs jobs and both companies were keen on

hiring me. I was really keen on joining the medical device company that I had interviewed for. But right at that time, life took an unexpected turn for the entire world, and suddenly we were in the middle of the corona pandemic. There was an immediate hiring freeze for most companies and no further communication from both the companies.

I started losing a lot of sleep over my job search as my visa was limited. But extraordinary times demand more initiative and creativity, and I kept thinking about how I could convince the company I was interested in. Just to show my initiative and commitment, I wrote up a piece analysing the company's products with its competitor products. My PhD had trained me very well on scientific evaluation and I could leverage on that experience. And, sure enough, this struck a chord with the hiring manager. He gave me a job offer that very day. This was a lesson for a lifetime – failures and extraordinary times can bring out the best in us. It helps us to be creative and take bold steps. And that is my message to everyone – go out there and be bold, pursue opportunities, and opportunities will pursue you.

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"I had two job interviews for regulatory affairs jobs ... then life took an unexpected turn for the entire world and suddenly we were in the middle of the corona pandemic."

**Foreword:** Diana's article first appeared on Health Writer Hub and is reprinted with permission. Diana is a member of the Health Writer Hub Alumni. Established in 2014, Health Writer Hub is an online education resource for aspiring health writers. Our health writing courses teach you how to create high-quality, evidence-based, easy-to-understand health content. And, because all courses are accredited, independently certified with The CPD Certification Service, you can be confident you're signing up for a quality programme when you enrol. Health Writer

Hub students strive to enhance global health literacy levels and improve health outcomes by creating best-practice, life-changing health content. Passionate about inspiring behaviour change through effective communication, we believe high-quality health writing plays a significant role in creating better public health. Since 2014, more than 1000 students from around the world have taken a Health Writer Hub course. And, at last count, Health Writer Hub students represented 40 countries! Health Writer Hub students are aspiring writers, experienced writers, health

communicators transitioning from an employed role, health professionals, physicians, PhDs and freelancers keen to specialise in health & medical writing. Our Alumni are writers who want to work full-time, part-time, in addition to clinical work and around family commitments. If you're driven by the desire to make a real difference in people's lives through effective communication, visit [healthwriterhub.com](http://healthwriterhub.com).

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## From pharmacist to medical writer

If you had told my 16-year self that I would become a pharmacist, working at a community pharmacy, I would have been delighted. A respectable, high paying (at the time) job, helping others, and keeping in touch with the latest scientific developments was everything I was aiming for.

If you then told me I would graduate from pharmacy school only at 31 years old, after another degree, 10 years as a pharmacy technician, and that I would have a newborn in my arms, I would start to question your sanity.

If you ended the story by telling me that I wouldn't want to work as a respectable pharmacist in a safe job and instead choose to start a career in a semi-obscure field, working as a freelance medical writer...well, in that case I would smile politely and walk away from you. Slowly.

### The wondering pharmacist

I entered the pharmaceutical sciences course knowing I would like to have more options than to work behind a pharmacy counter. While I liked to bridge the gap between scientific knowledge and information that patients actually understand, there were many things that started to grate my nerves. None of those things was related with communication or the human connection with other people, but with management issues, so I started looking for careers in the pharmaceutical industry.

I'd always liked the drug development process, and some of my colleagues had found

roles as clinical research associates (CRAs), working in clinical trials. They said it was a fast-paced industry, with potential of career development, so I decided to do the same.

I applied for a few roles and enrolled in a CRA course aimed at medical and scientific professionals that wanted to increase their chances of getting hired. In the lecture about clinical trial protocols, the instructor had a job title I'd never heard about: medical writer. Hmm.

### Work-life balance

When I finished the CRA course, I faced a challenge that many people have when they try to enter the market: it's hard to get a job when you have no experience. It's hard to get experience if you don't have a job. Internships are one way

to get experience, but they're not easy to get into when you're over 30 years old. An unpaid internship would also mean I would have to leave my paid job. Not ideal.

I was also finding out that some roles, like CRA or medical science liaison, require frequent travel. At this point of my life, having small children, I would prefer to stay close to home.

I decided to know more about that mysterious role I learned about in the CRA course, connected with some medical writers through

Writing is a learnable skill, and one that gets better with practice... but transitioning would require a plan, hard work, and some helpful resources.

LinkedIn, and asked them some questions:

- How did they become medical writers?
- Did they like it?
- What advice would they give someone trying to get into medical writing?

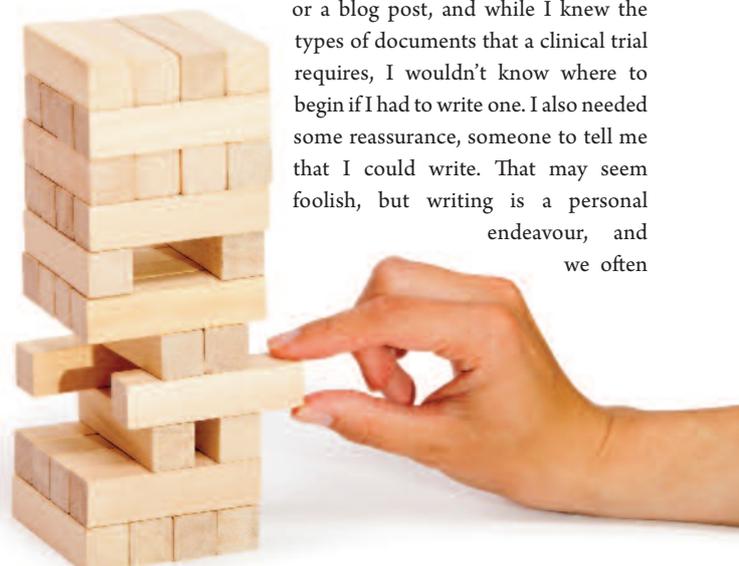
All the medical writers in my network were extremely helpful, giving me resources to explore and a word of encouragement. To continue this tradition, I make a point of replying to every message aspiring medical writers send me.

Slowly, I started to think that it was possible to combine working at home as a medical writing and having enough flexibility to spend more time with my family. It would require a plan, hard work, and some helpful resources.

### Learning how to write

My time in university taught me how to read scientific papers and understand medical jargon, and through the work at the pharmacy I learned how to communicate complex science in simpler terms.

But I didn't know how to write a news article or a blog post, and while I knew the types of documents that a clinical trial requires, I wouldn't know where to begin if I had to write one. I also needed some reassurance, someone to tell me that I could write. That may seem foolish, but writing is a personal endeavour, and we often





feel exposed when we show our work to the world.

Thankfully, writing is a learnable skill, and one that gets better with practice, so I scoured the internet for online or local courses where I could learn the basics of medical writing.

I started with Coursera's Writing in the Sciences, a well-rounded and comprehensive course. It's mostly aimed at academic writing, but it also teaches how to edit ruthlessly (a necessary evil for most writers) and how to write a news article.

Next, I found Health Writer Hub. Starting in a month, the March "Introduction to Health Writing" course was perfectly timed, and Michele's encouraging feedback was the nudge that I needed to start calling myself a medical writer.

## Life as a freelance medical writer

Usually, freelancers work for some years in a pharmaceutical company or in a contract research organisation before going out on their own. By then, they have mastered the basics, they know how long it takes them to produce each document, and they have some contacts that can pass on work.

I had none of that.

To overcome these obstacles, I joined the

EMWA. This professional organisation provides education, resources, and networking opportunities to its members. In 2019, I attended the two conferences EMWA held, in May and November. This allowed me to participate in several workshops and, more importantly, to network with other medical writers, both seasoned and newbies like me. The environment at these conferences is very relaxed, and everyone is nice and keen to help fellow writers.

After a while, I wrote my first article for the association's journal. I co-wrote it with another medical writer that I contacted through LinkedIn and which is now my virtual friend and colleague. When his company needed a proofreader with knowledge of English and Spanish on short notice, he put my name forward and I did that project.

Through interaction with another medical writer and colleague in the EMWA webinar team, I got the chance to make a trial for a local branch of an international medical publishing company. They liked my work and I am now waiting for some regular projects from them.

Networking has been the main way for me to find work. It has also led to meaningful connections and good conversations, an important aspect for those who don't have co-workers to chat with.

There are also other ways to find work, of

course. I have a profile on Kolabtree and I'll soon invest in some niche freelance directories, but so far what has worked for me is networking, volunteering for EMWA, and having a newsletter that showcases my writing style.

## What now?

My journey as a freelance medical writer has just begun. I will keep learning about writing, new developments in drug development, and my new passion: medical devices. I hope my story illustrates the diverse backgrounds medical writers can have, and I hope that you can draw some inspiration from it for your own path.

**Diana Ribeiro**

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# Lingua Franca and Beyond

## Tower of Babel – speaking different languages and still striving to communicate

### SECTION EDITOR



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The story in the Bible goes: “a united human race in the generations following the Great Flood, speaking a single language and migrating westward, comes to the land of Shinar (שִׁנְאָר). There they agree to build a city and a tower tall enough to reach heaven. God, observing their city and tower, confounds their speech so that they can no longer understand each other, and scatters them around the world.”<sup>1</sup>

Is it true or not? Most likely not; there are many hypotheses about the origin of languages and no definitive answer. We need to agree upon one thing though – a language spoken by a certain group of people reflects their mentality or possibly the other way around: their mentality shapes their language.

I have always been fascinated by linguistic variety and interference. One of the phenomena that particularly caught my attention was Finnish – why and how is it so different from the languages spoken in neighbour countries?

However, before getting to my Finnish point, I owe a short explanation. I am a passive (☹) member of the European Association of Science Editors, and in a lengthy email discussion about the proper use of “fewer” or “less”, I saw Carol’s comment “always remembering growing up in a Florida tourist town with, this year, ‘less tourists or more’. ...” and her signature:

*Carol*

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Well, I thought, I need to ask her if she would like to contribute to our “Lingua Franca” section and have her take us through her English–Finnish adventure. Fortunately, Carol agreed and here we are!

Just a few words about Carol: as already said, she is an American from Florida, who moved to Finland in 1985, ran and walked the Helsinki City Marathon at age 47 in 5.25 hours, loves fast Finnish ballroom dancing, and for almost 20 years in the USA she wrote fiction, wrote about deafness and created the first ostomy-surgery PR material. As Carol says: “I showed the comical side (*cul de sac*, marsupial us), back when many tended toward suicide.” The rest you will read in her superb and very entertaining text, and please do remember that “The main point of this tale is the huge chasm between Finnish and English and its reflection in the Finnish character”.

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**Maria Koltowska-Häggström**

# An American lucky to be among Finns

In 1985, I began creating the University of Helsinki's first course in English writing for research scientists, decades before I discovered this great tip: Aim for short words in short sentences in short paragraphs.<sup>1</sup> How Finns wrote was the opposite: long paragraphs of long sentences with lengthy agglutinated words with complex case endings (16 cases each for singular and plural; prepositions non-existent). A famously long word in English is *antidisestablishmentarianism*, but in Finnish one meets *useampimerkityksisten tietosuojakäytäntöjen avulla* (to show Finnish word order and absence of prepositions. It means more than many meanings of multi-use data-security practices... with the aid of). Recognisable cognates of Indo-European words are few – though some words grow an *i*, like *grilli* (grill) or *filmi* (film); *pankki* is also recognisable (bank). Articles? None. Pronoun gender? Absolutely none here, where women voted in 1906!

One notorious novelty involves a Finnish farmer asking his farmhand *Kokko* to gather a whole pile of hay, and the boy asks “Whole pile?” This gives us “*Kokko, kokoo koko koko. Koko kokoko?*” Every initial syllable invariably has heavy stress, and all double letters lengthen. Good luck! Or how about this seven-vowel (yes, including “y” here), three-word union meaning “wedding-night intention”: *häyyöaie?*

Half my students were, from Day One, physicians. I, too, had chosen to study medicine, hoping in part to fulfil my grandfather's abandoned goal. As a medical student, he heard his US president vow to free the slaves, and thus he joined Lincoln's army. Badly injured, he left school, became an insurance agent, and, as an old man, fathered four girls. My pre-med bachelor's degree (biology/chemistry) at Duke University qualified me for its medical school, but with zero funding, I instead worked in one of its research labs, handling drug-resistant tuberculosis. After Oak Ridge National Laboratory and “sacrificing” a thousand mice, I switched to writing, my second love. I'd written my first story at 7 and a novelette at 13 in typing class, so I breezed through an MA in rhetoric, and in my PhD thesis (University of Maryland), I analysed “The Image of the Physician in Literature.” By age 50, I had produced eight novels and a handful of articles.

During our degree-studies, I taught writing in universities and colleges for 7 years. I then accompanied my botanist husband Dan on three herbarium visits to Finland; the fourth trip was

his Fulbright-scholar year. Loving Finland, we both decided to stay. When, however, our third course in Finnish introduced case endings also for *verbs*, Dan (who had excelled in years of school Latin) threw up his hands and went home to California. Unlike Dan's department, my language centre was full of English speakers. Having neither kids nor siblings, I decided to hold on to my Dream-of-a-Lifetime Job. I refused to leave; I demurred.

Flash forward almost 10 years to 1995, when, as he neared 50, a physicist named Jyrki (which is, amazingly, pronounced YEAR-key) started studying English with me, and one might say he never ceased! In return, however, he enlightens me constantly on inter-language differences. Our home language, by his choice and my necessity, is English, and I also listen constantly to English broadcasts to preserve my English ear.

Back to 1985, when I unexpectedly yet permanently left a nation of 300 million people for one of 5 million. What flew into my hands was a just-published, heavy-in-every-respect guidebook subtitled “for Finnish scientists writing in English”. The author of this book, *The Words Between*<sup>2</sup> was Peggy Perttunen (1916–2016), an English botanist who had tutored a tall, shy Finnish entomologist. She soon found herself in Finland – for the first time – as his wedding-cake-bearing new bride. Within one week, the Peggy who had 2 years earlier been a rooftop warplane-spotter became an author's editor at the nearby University Hospital. Her immigrant-to-Finland tale thus far outdoes mine.

Finland's excellent education system, coupled with what I suspect is high intelligence, means that Finns' written English can surprise Indo-European speakers. I shelved plans to teach grammar the way I taught it to US university undergraduates. Peggy – once overheard saying “Carol is American, but she's very nice!” – showed me what Finnish linguistic interference was: lines like “Every ninth patient died”, “Darwin published her major book in 1859”, and “The other eye was affected but not the other eye”. Journal editors abroad, accustomed to everyone's errors in preposition and article choice, would surely be perplexed by such lines.

I tell students and editing clients, endearingly embarrassed by making errors, that the fault is not really theirs. Finnish is an isolated, conservative, still completely logical language, persisting despite Swedish conquerors' attempts to disallow and suppress it. English, conversely,



Carolyn  
Brimley Norris

Photo: Carolyn (Carol) Brimley Norris in 2017

sprouted like a field of weeds on an oft-invaded island forced to develop continuously evolving constructions. Written Finnish first appeared in Mikael Agricola's *abc-book* of 1543, but waited 320 years to become Finland's official language, 7 years before the first-ever Finnish novel, which has its own annual day of honour.

My first students here asked about British versus US English spelling, since in Finnish, each letter represents one phoneme. And how can our preposition choices (living/playing *in/on* the street) also differ? Finns are also stunned that English syllable-stress may in mere decades migrate (*contribute* to *contribute*) and can even hop around for emphasis (She wed at *thirteen?*). England has regional dialects, America regional accents, and Finland has both, but also *kirjakieli* and *puhekieli*, its *book-* and *spoken-* Finnish. Before 2000, Finnish courses for foreigners ignored the spoken Finnish as low. I never learned it; I constantly overhear it. The rules of Finnish demand from foreigners only prodigious memories. Ancient rules hold always! *Aina!*

Peggy edited for the university medical faculty until age 86; I fondly remember her in a large, overstuffed chair, on her lap the manuscript PhD thesis of the paediatrician who perched on one chair-arm, as I perched on the other. Peggy raised children and taught her clients informally. My original university writing course has continued happily – without one semester's break – for 35 years. Teaching for the Language Centre also included oral English courses for medical, dental, and veterinary undergraduates. When Finns began attending more meetings abroad, I added a medical-faculty conference-

presentation course. Finns were submitting articles mainly to Nordic journals, but soon had articles appearing in the UK and USA. Their findings proved important; what their texts needed was a clearer, more concise and powerful style.

Peggy had long championed active voice and end-focus, explaining that the bulky, boring English passive<sup>3</sup> differs from the Finnish passive, which is a single word, frequent but innocuous, like replacing *minä tein sen* (= I did it) with *tehtiin* (= it was done). With similar modesty, Finns conceal exciting ideas or findings in each sentence's dead centre. Both habits – along with silence and eye-contact avoidance – may exemplify the national character. Shyness is, however, not meekness; in 1939–1940, Finnish courage, *sisu*, empowered troops to beat back a large eastern invader, although outnumbered 10 to 1.

My course materials grew from paper handouts into an 85-page book.<sup>4</sup> One of its exercises requires reducing a 200-word Finnish Methods section by half, putting its 14 passive-voice verbs into the active without “we”, and flipping over clauses to achieve end-focus. With the tool of inanimate agent (the test served, data provided) Finns learn to enjoy doing this.

At exactly the right moment, my second mentor, Björn Gustavii, MD, PhD, of Sweden (1932–2019), saw his delightful Lund University science-writing guide soar to its 2003 publication by Cambridge University Press.<sup>5</sup> (It had first been published by Studentlittertur in 2000.) Equally invaluable was Björn's first-ever guide<sup>6</sup> to the compilation PhD thesis that Finnish and Swedish scientists prefer. For a dozen years, I tweaked Björn's English, and he factually enriched my unpublished course book ... without our ever meeting. Overloaded emails, but alas, no overstuffed chair.

Occasionally I consult with professors for whom I author-edit, but daily I edit post-course manuscripts for my students. These become journal articles for their compilation PhD theses. Later, I am the sole editor of their up-to-100-page thesis summary or analysis, the *yhteenveto* (= together drawing). This produces a bound book including their four or five articles in international medical journals, and it underpins a frighteningly formal public thesis defence. The *yhteenveto* then goes forth into the world as an e-thesis. Some literature sections of the *yhteenveto* can shrink into review articles.

Finns scoff at their thrice-won title “The World's Happiest People”, another saying being “If people on the street smile at you, they're either crazy, drunk, or American.”

Recently, a professor friend sent me his student's lengthy *yhteenveto* in surgery that presented a unique problem: it was in Finnish, but to be accessible worldwide it had to be in English. Those 100 pages therefore passed through Google Translate; the professor did his best with the result, and I did more. Google – though steadily improving – finds Finno-Ugric languages (which include Estonian and Hungarian) still a challenge. One recipient of my annual letter (no social media for me!) asked Google to translate it into Finnish. Its back-translation into English had me falling about, laughing.

Despite my limitations, the immigration office issued me a passport in 2005 on the basis of Finland's 4-hour language exam – its sole requirement for citizenship. After 20 years here, I had achieved the minimal score of 3/6! Finland's other official language is Swedish. Unlike Canada, where French-speakers are 21% of the population, Swedish speakers here account for only 5%. (Sweden and then Russia owned Finland, making us only 103 years old.) English, however, wins the prestige prize, and America has been a role model, though American English only after the 1980s, when US TV swamped schools' “English English”.

Fluent English speakers in southern Finland – most everyone under 60 – hear one word from me, like *kiitos* (= thank you), and usually ask me to speak English. This is no insult; no Finn has ever criticised my attempts. Some Finns yearn to practice spoken English, explaining, “Good Finnish is so hard to speak, why try?” They do feel guilty pride in their language's difficulty. *Selkosuomi* (= clear Finnish), mercifully on offer, I grasp easily. Whereas I studied Cuban Spanish at 15 and French in college, foreign languages start here at 7, usually English. Then comes Swedish, and many tackle a few more. Language learning actually begins in utero, thanks to undubbed TV and films, a wise Nordic practice (true also of the Netherlands). Post-utero, a baby's early words worldwide are variations on “mama” and “papa”, natural mouth movements. Our clever babies instead manage *äiti* (eye-tea) and *isä* (ee-seh).

My chief advice is therefore “Never translate lines from Finnish into English, and before sending manuscripts to journals or to me, read them aloud to yourself, trusting your lifetime-trained ear.”

How fortunate I am to teach English writing skills and to author-edit for my own students,

whether they are age 25 or now retired (as I hope I shall never be). Then, editing shows me what I should currently teach, like punctuation, still, and avoidance of naïve, unintended plagiarism. Increasingly, students come from abroad, now comprising about one-fifth of my classes, their differing issues quickly recognisable. Persians and Nepalese are particularly good non-Indo-European writers; Estonians from across our narrow strait write just like Finns.

Finns scoff at their thrice-won title “The World's Happiest People”, another saying being “If people on the street smile at you, they're either crazy, drunk, or American”. But before COVID-19 made us all learn to teach remotely, I was able, on each final day of class, to hug all of my smiling medics – a privilege of *lil ole ladies*. Finns' efficiency, honesty, and high respect for learning – and for teachers – will surely survive time and viruses. Luckily for me.

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*Carol's book Academic Writing in English is updated annually. Write to Carol to receive 30 pages of keys to exercises in the book.*

# My First Medical Writing

## Editorial

In this release of My First Medical Writing, I have the pleasure to share with you a great article written by aspiring medical writer Shirene Melissa Singh. With over 5 years of experience as a university educator and researcher, she is

passionate about writing about infectious diseases, immunological concepts, global health perspectives, and applied research. In this article, Shirene shares not only her knowledge but also her views on the current COVID-19 pandemic,

in a very thorough and engaging manner that leaves the reader with a lot of food for thought. It has been a pleasure working with Shirene on her first article in *Medical Writing*.

**Evguenia Alechine**

## Quarantine and isolation: Double-edged sword or imperative?

Quarantine and isolation practices are vital components of public health interventions aimed at minimising virus spread during the COVID-19 pandemic. As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) took its toll globally, stringent measures were implemented by several affected countries in order to restrict population movement. In a coordinated response, many countries focused on minimising the impact of the pandemic by reducing global levels of morbidity and mortality. Through a lowering of the degree of population mixing in the delay and mitigation phases of the pandemic, peak numbers of infected individuals were projected to be reduced at a given period. This concept, also known as “flattening the curve”, is designed to prevent health care systems from becoming overwhelmed. Quarantine and isolation practices, while undisputedly important are not without challenges that relate to compliance and sustainability.

Historically, quarantine and isolation were used from as early as the 14th century in the Black Death epidemic. Later, during the 18th century these measures were incorporated for disease control against a cholera outbreak. Quarantine, considered as paramount for the successful control of contagious diseases, was frequently implemented with other public health measures including isolation.<sup>1</sup> In modern public health terms, quarantine is used to describe the separation of individuals through movement restrictions over the incubation period after potential exposure to a contagious disease.<sup>2</sup> This course of action is deemed necessary to minimise the possible risk of spreading that disease to susceptible members of a population. Isolation refers to the separation of infected individuals

through movement restrictions specifically for those confirmed as having a contagious disease. Contact tracing is done concurrently with quarantine and isolation to identify individuals that have been potentially exposed to a contagious disease. These public health principles have successfully stood the test of time. The intuitive question is how pertinent are such principles to the COVID-19 pandemic and why?

To address this question it is necessary to understand key concepts. Unlike the four major human coronavirus types (229E, NL63, OC43, AND HKU1), which are sometimes associated with the “common cold,” SARS-CoV-2 is a novel coronavirus.<sup>3</sup> This means that prior to the initial outbreak of COVID-19, immunity did not exist in the global population. The situation was further compounded by a lack of existence of approved, internationally-licensed vaccines, and efficacious antiviral drugs.<sup>4</sup> Additionally, diagnostic testing was initially restricted to molecular tests. Due to the unavailability of reliable serological tests at the time, protective immunity could not be measured. Concerns later developed regarding virus transmission in pre-symptomatic and asymptomatic individuals. Since respiratory droplet transmission was not restricted to clinically infected individuals only, virus containment posed a challenge regarding COVID-19.<sup>5</sup> The basic reproduction number (R0) of SARS-CoV-2 represents the average number of new infections produced by an infected individual in a population with no pre-existing immunity. Therefore, in a susceptible population herd immunity is not immediately possible since this requires the development of protective immunity in a certain proportion of the population over time. Several estimates of R0 have been reported

for SARS-CoV-2 based on current data.<sup>6</sup> However, a preliminary estimate of 1.4 to 2.5 was provided by the World-Health Organization in January 2020, based on available data at that time.<sup>7</sup> This estimate provides an indication of the severity of spread of COVID-19. At the onset, since R0 was greater than 1, the number of infected individuals in a susceptible population was expected to increase. In this regard, public health interventions such as quarantine, isolation, social distancing, use of personal protective equipment, and cough and hand hygiene became necessary to reduce exposure risks.

Concerns have been expressed over the feasibility of prolonged, widespread implementation of quarantine and isolation measures. The imminent threat of a global recession linked to factors such as loss of income, unemployment, trade, manufacturing, and international travel disruptions must be considered.<sup>8</sup> Predicting the medium to long-term macroeconomic impact of the COVID-19 pandemic on developed and developing countries remains a challenge. Equally challenging is predicting the course of recovery of productivity and economic growth. From a microeconomic standpoint, extensive restrictive measures can be problematic for individuals earning low wages and who are not entitled to paid sick leave or unemployment benefits. Further concerns have been expressed over the disproportionate increase in women’s unemployment rates compared to men’s in the United Kingdom and the United States of America.<sup>9</sup>

The success of China’s response strategy to COVID-19 is largely attributed to population compliance with stringent restrictive measures. Many Western countries have opted for a similar

## SECTION EDITOR



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Historically, quarantine and isolation were used from as early as the 14th century in the Black Death epidemic.

strategy involving extensive lockdowns with the exception of Sweden that supported voluntary measures.<sup>10</sup> Nonetheless, prolonged implementation of these measures may prove difficult due to perceived infringements on the constitutional rights of individuals. The psychological impact of prolonged quarantine and isolation must be carefully considered especially for societal groups such as the elderly, students, and victims of domestic abuse. In these instances, effective support systems for minimising anxiety and depression and close monitoring of susceptible individuals become imperative.

As the pandemic runs its course we would, inevitably, learn several lessons along the way. Striking the right balance between protecting the population's health and promoting economic growth is no easy task to endure. Furthermore, there is an opportunity to reflect on moral dimensions of the pandemic. One question that we need to ask ourselves is, "Does the right to freedom of movement by individuals outweigh society's obligation to protect the elderly?" Perhaps there is no "one size fits all" solution to this issue. Until then, contemplation of the old adage "prevention is better than cure," may be in order. A collaborative, interdisciplinary "One World, One Health" approach promotes closer monitoring of zoonotic viruses and therefore better pandemic preparedness.

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# In the Bookstores

## Coronavirus: A book for Children

Written by Elizabeth Jenner,  
Kate Wilson, and Nia Roberts  
Illustrated by Axel Scheffler.

ISBN: 9781839941467

Publisher: Nosy Crow Ltd

15 pages

Free to download from

[https://dlcs.io/file/wellcome/5/b3226382x\\_0001.pdf](https://dlcs.io/file/wellcome/5/b3226382x_0001.pdf)

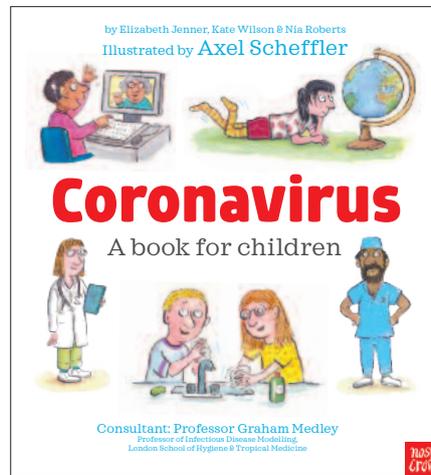
The Wellcome Collection, as part of the Wellcome Trust, operates a free museum and library in London dedicated to science and health. Through curated exhibitions, broadcasting, and publishing, as well as digital works and an art collection, the Wellcome Collection explores “medicine, life and art” (<https://wellcomecollection.org/>).

As part of their remit, they provide online access to “freely licensed digital books, artworks, photos and images of historical library materials and museum objects”, and their online repository is an interesting and eclectic mix of health-related “ephemera”. This includes an array of past health campaigns from around the world alongside more modern equivalents. The ability to adapt and write for your audience is a key skill for any medical writer and this collection presents many examples illustrating the use of different communication styles that have been used to inform health campaigns and their respective audience.

Although Sir Henry Wellcome acquired the bulk of the Wellcome Collection between 1890 and 1936, the collection has been expanded year on year and includes current health-related ephemera. For example, there are over 2000 items related to tuberculosis in the form of books, digital images, pictures, ephemera and videos in the date range 1659 (an academic dissertation) through to 2018 (four watercolour paintings for a comic strip about bovine tuberculosis in the UK).

Dating from 1986 onwards, more than 5000 items in the repository are associated with campaigns designed to combat the threat of HIV and AIDS associated with untreated HIV infection. Around 1987, when the public had great fears about this new and unknown virus, a seminal UK health campaign was conducted to promote public

It is a good example of writing about health in a way that children can easily relate to and understand.



awareness of the virus and AIDS. Items related to a government AIDS health campaign can be viewed in the Wellcome Collection, including the UK government-produced leaflet called “AIDS: Don’t Die of Ignorance.” At the time a copy of this leaflet was sent to all British households to inform them about the disease. Information in this pamphlet was presented to the reader in plain black type, in the form of a series of 10 questions and answers (<https://wellcomecollection.org/works/fd7ab5tc>). The answer to Question 2: Why should you be concerned about AIDS? includes the stark statement “There is no cure, and it kills.” Alongside the leaflet, there was a video advert called “AIDS iceberg”, which featured a black, marble headstone with letters being chiselled out, and when finished, the headstone falls to the ground revealing the word AIDS (<https://wellcomecollection.org/works/d3us7ffp>). This campaign did not use colour images, nor did it use cartoons or humour; it was clearly designed to strike a sombre, dark and apocalyptic note.

In stark contrast, and coming right up to date, there is a downloadable book entitled *Coronavirus: A Book for Children* written by Elizabeth Jenner, Kate Wilson, and Nia Roberts with illustrations by Axel Scheffler ([https://dlcs.io/file/wellcome/5/b3226382x\\_0001.pdf](https://dlcs.io/file/wellcome/5/b3226382x_0001.pdf)). The content of the book is aimed at primary age children. It is free to download and explains what a coronavirus is, the types of symptoms you might have if you catch the virus, how you might catch it, and what

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happens if you do. The book is brightly coloured, has impish drawings, and is written in an upbeat manner. It is designed to inform the reader by presenting information about the virus in a non-threatening and enjoyable way. The information is displayed in small bite-sized pieces to explain and not frighten or talk down to the reader.

The authors explain why people are so worried about the coronavirus, whether there is a cure coming, and what everyone can do to help stop the spread of the virus. They don’t shy away from explaining complex scientific concepts and include a description of antibodies and how they help fight infection:

The body has an amazing weapon against viruses called antibodies. Tiny cells in your blood make antibodies to fight each different virus invader. The antibodies catch the viruses, then the blood cells swallow them up and destroy them and then the person gets better.

This is a well-written, beautifully illustrated downloadable pdf book. It is a good example of writing about health in a way that children can easily relate to and understand. Most importantly it is designed to allay their fears and is in complete contrast to the “AIDS: Don’t Die of Ignorance” campaign from over 30 years ago.

I look forward to viewing the health literature that the Wellcome Collection will undoubtedly accumulate on the coronavirus pandemic. I can’t help but wonder what future medical writers might say about the tenor and content of the coronavirus health campaign 30 years from now.

As the authors say in their children’s coronavirus book, “One day, this strange time will be over.” In the meantime, I hope you all stay safe and well.

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## Images from the Wellcome Collection

Several images from the Wellcome Collection have been brought together to reflect themes and short photo stories created around them. Dr Estelle Paranque's short photo story entitled "The Celebrity Physician and the Plague" presents an outline of the life of Charles de Lome (1584–1678) a 17th century doctor who invented the "plague prevention costume". Paranque's article is illustrated by a series of pictures illuminating "plague prevention" clothing that Charles de Lome and others adapted to protect themselves from infectious diseases through the ages.

Dr Paranque writes, "This costume covered the person wearing it from head to toe so that the air – which carried dangerous viruses and germs – could not penetrate, offering a layer of protection to doctors as they attended the sick." You can clearly see that the 17th century outfit is a precursor to the full personal protective equipment that health care professionals are wearing to treat COVID-19 patients in our hospitals today (see pictures at <https://wellcomecollection.org/articles/XvBkkhAAACIAu441>).

*A physician wearing a 17th century "plague prevention costume".*



## Social media

For many people social media has become a primary source of information, including that related to medicine and healthcare. This issue will include articles about this trend, how to leverage the different social media tools, and how to write for social media.

**Guest Editor: Diana Ribeiro**

The deadline for feature articles is December 8, 2020.

## The March 2021 edition

**Don't miss!**

# Good Writing Practice

## Grammatical disagreement in number

### Introduction

The disagreement in number (singular vs. plural) between subject and verb is caused by subject number ambiguity, either intrinsic (the subject itself) or extrinsic (the effect of subject modification).

### Experimental sections

#### Part 1 – Materials and methods section: Methods

##### Example: Singular subject number intrinsic ambiguity

After 5 min, 20  $\mu\text{L}$  [*was or were*] injected into the hemacytometer, and cells were counted.

##### Revision

After 5 min, **one volume** (20  $\mu\text{L}$ ) was injected into the hemacytometer, and cells were counted.

##### Notes

Singular in symbol form ( $\mu\text{L}$ ) but pronounced as a plural (*microliters*), what is the grammatical number of a volume? If the focus is on the entire volume 20  $\mu\text{L}$  being injected rather than increments, the singular verb *was* is grammatically correct. However, if it is inexplicit whether the injection is all at once or incremental, this ambiguity can be lexically resolved. Analogously, the symbol for grams (g) is also singular in form but plural in pronunciation.

#### Part 2 – Materials and methods section: Methods

##### Example: singular subject number extrinsic ambiguity

The subcellular location of the truncated subunits [*was or were*] identified.

##### Revision

The truncated-subunit subcellular location **was** identified.

##### Notes

Does an intervening prepositional phrase with a plural object affect the number of a singular abstract subject? *Location* is the subject not *subunits*. The distraction results from the proximity

between the plural object *subunits* and the singular verb. In the example, the verb number is the grammatically correct singular. However, the proximity of the plural *subunits* and the singular *was* is still distracting. In the revision, the merging of the modifiers into a singular premodifier obviates any disagreement in number.

In contrast, does an intervening prepositional phrase with a singular object affect verb number of a plural subject? *Different channel estimates in the APML algorithm correspond to a different time interval*. The plural subject *estimates* is undistracted by the singularity of the post-modifier *algorithm*.

Another example (Materials and Methods: method) reinforces the principle of extrinsic modified subject number uncertainty. A *sample of 50 patients (age 25-50 yr) with a history of focal epilepsy [was or were] examined*. To avoid confusion between the singularity of *sample* and the plurality of *patients*, *sample* can be deleted. This deletion will avoid the conflict between the grammatical correctness of the singular and the rhetorical (notional) effect of the plural. *Patients (age, 25-50 yr; n=50) with a history of focal epilepsy were examined*.

Consider also this example (from the Results section) that involves a quantifier (e.g., *majority*). *The majority of the proteins was eluted with 1 M NaCl* can be revised by using a more explicit subject; that is, **Most of the proteins were eluted with 1 M NaCl**. Other such weakly inexplicit quantifiers are *a number of*; *a percentage of*; *a range of*; *a variety of*. For all, a numerical substitute (e.g., a numerical range or approximation) would eliminate the agreement in number uncertainty. *For example, the proteins (50-60% of the total number) were eluted with 1 M NaCl*.

#### Part 3 – Materials and methods section: Materials

##### Example: Singular pre-noun modifier-caused subject plural number ambiguity

Each rat and mouse [*was or were*] diabetic.

##### Revision

Each **animal** (*rat, mouse*) was diabetic.

##### Notes

What effect of the singular determiner (indefinite

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pronoun) *each* on plural coordinate nouns have on verb number? The singularity of *each* prevails despite its reference to coordinated nouns, because the focus is on the individuality of each noun of the pair. However, in the revision any uncertainty is resolved by subsuming under a singular noun.

The effect on verb number is the same when *each* occurs after the coordinated nouns: *The erythrocyte fraction and the plasma fraction each contains linoleic acid*. However, the possibility of verb singularity or plurality causes a distraction, which can be avoided by post-noun to pre-noun, transposition, coordinated fractions, and subsuming under the singular *fraction*: *Each fraction (erythrocyte, plasma) contains linoleic acid*.

Some indefinite pronouns (functioning as determiners) are decidedly singular (*each mussel*). The singularity of other determiners is less explicit, for example, *every*. However, *every* is singular emphasising an item being part of a group (*every mussel was analysed*). In contrast, the indefinite pronoun *none* is ambiguous as in *none of the isomers [contain or contains] radioactivity*. *None* can mean *not one* (singular) or *not any* (plural). Consequently, to avoid such ambiguity, either of these substitutes is preferable to *none*.

#### Part 4 – Results section: Data verbalisation

##### Example: Proximal singular and distal plural noun number ambiguity

There [*was or were*] a monomer and several dimers.

##### Revision

There was a **combination** (*monomer, several dimers*) present.

##### Notes

In the example, coordinated subjects of a

different grammatical number (i.e., *monomer* and *dimers*) in a *there-delayed subject* sentence, results in the verb *were* misagreement in number to the proximal subject *monomer*. The alternative *there was a monomer and several dimers* is correct as to proximity of verb and subject, but not as to the coordinated subjects. However, the proximity correctness seems to overrule the coordination incorrectness. In contrast, subsuming under the singular *combination* is an explicit lexical alternative.

In another example the revision is also to place a summative number before the list: *There [was or were] a tRNA, mRNA, and rRNA. There were three RNAs: tRNA, mRNA, and rRNA.* Insertion of *three RNAs* enables the verb *were* to agree proximally and coordinately with *three RNAs*. Also, subsuming eliminates the misagreement of *a* (instead of *an*) with *mRNA* and *rRNA*.

## Contextual sections

### Part 1 – Introduction section: Research problem pertinent background

#### Example: Singular subject number intrinsic ambiguity

No data [is or are] transmitted during the guard time.

#### Revision

Not any data are transmitted during the guard time.

#### Notes

Grammatical number ambiguity is caused by a Latinate plural noun (*data*). Traditionally *data* is considered a plural count noun, as in *many data are transmitted*. However, *data* can be considered as a collective (i.e., a singular) equivalent to *information*, enabling *much* (not *many*) *data* to be acceptable.



The stricture on *data* being only plural and *datum* singular is, however, relaxed for the Latin *agenda*. Rarely is the Latinate singular *agendum* used instead of the plural *agenda*. For example, no one says *what are the agenda today?* Thus, *data* can be both a collective singular as well as a plural; however, traditionalists will likely be distracted by a *data* singular usage. In contrast, *not any* is unequivocally plural.

### Part 2 – Introduction section: Research problem pertinent background

#### Example: Coordinated nouns intrinsic singular subject number ambiguity

Traditionally, *orthodontic diagnosis and treatment* [is or are] taught and practised as a descriptive qualitative subject.

#### Revision

Traditionally, *orthodontic management* (*diagnosis and treatment*) is taught and practised as a descriptive, qualitative subject.

#### Notes

How do coordinated nouns that are intended to function as a single unit affect verb number? Analogous to *a knife and a fork* is, *diagnosis and treatment* is intended as a singular unit requiring a singular verb. The subtlety and infrequency of the collective meaning will elicit questions as to the grammatical correctness, which is rendered explicit in the revision by subsuming the coordinated nouns under the singular term *orthodontic management*.

#### Summary

Insight may be gained from the intrinsic and extrinsic perspective because reliance on the rules of grammar may still result in the ambiguity of agreement in number between subject and verb. Instead, lexical alternatives (e.g., a singular summative subject) or an explicit subject (singular or plural) may resolve the ambiguity.

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## Schematised misagreement in number distractions and preferred revisions

### Intrinsic subject number ambiguity

After 5 min, 20 µL was injected into the hemacytometer, and cells were counted.

→ After 5 min, **one volume** (20 µL) was injected into the hemacytometer, and cells were counted.

No data are transmitted during the guard time.

→ **Not any** data are transmitted during the guard time.

Traditionally, *orthodontic diagnosis and treatment* is taught and practised as a descriptive qualitative subject.

→ Traditionally, **orthodontic management** (*diagnosis and treatment*) is taught and practised as a descriptive, qualitative subject.

There was a monomer and several dimers.

→ There was a **combination** (*monomer, several dimers*) present.

### Extrinsic subject number ambiguity

The subcellular location of the truncated subunits was identified.

→ The truncated-subunit subcellular location **was** identified.

Each rat and mouse was diabetic.

→ Each **animal** (*rat, mouse*) was diabetic.

# EMWA 2020

# Virtual Autumn Conference

**Registration is now open for EMWA's first virtual conference!  
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Due to the ongoing COVID-19 pandemic, EMWA's Executive Committee has decided to shift the Autumn conference this year to a virtual format.

**The virtual Autumn conference will be held November 4 through November 19.**

EMWA's Executive Committee, Professional Development Committee, and Head Office are currently working to deliver a live and interactive conference experience that you can attend from the safety of your own home or office.



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The virtual Autumn conference will feature the usual conference events, including:

- Workshops
- Opening session
- Symposium
- Freelance Business Forum

# Upcoming issues of **Medical Writing**



## **December 2020:**

### **Writing for patients**

This issue will feature articles from some of the key opinion leaders in the area of writing for patients. We will cover aspects such as the current state of information given to patients and how we can do this better, the role of the medical writer with patient associations, the patient voice in research publications and writing up patient-reported outcomes, writing for the internet, and how patient needs are being incorporated into traditional medical communications.

Guest Editors: Lisa Chamberlain James and Amy Whereat



## **March 2021:**

### **Social media**

For many people social media has become a primary source of information, including that related to medicine and healthcare. This issue will include articles about this trend, how to leverage the different social media tools, and how to write for social media.

Guest Editor: Diana Ribeiro

**The deadline for feature articles is December 8, 2020.**



## **June 2021:**

### **Mentorship**

No one is born a medical writer. This issue will explore the important role that mentorship plays in the professional development of medical writers.

Guest Editor: Clare Chang

**The deadline for feature articles is March 8, 2021.**

## **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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