

Volume 27 Number 2  
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# Medical Writing



## Public Disclosure

### Also in this issue...

- Harmonising format and style requirements for scientific and medical publications
- Winners of the Geoff Hall Scholarship Essay Competition
- Report on EMWA's Medical Device Symposium



EUROPEAN MEDICAL WRITERS ASSOCIATION



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**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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#### Editorial: Public disclosure 1

Alison McIntosh

#### President's Message 3

#### EMWA News 4

#### The Regulatory Public Disclosure Special Interest Group 6

#### Feature articles

#### Clinical trial disclosure and transparency: Regulation EU No. 536/2014 Public disclosure at the clinical trial level 7

Kathy B. Thomas

#### Navigating the EMA clinical data website 19

Raquel Billiones and Achim Schneider

#### Anonymisation reports from 2016 to 2017: A preliminary analysis 22

Raquel Billiones

#### Preparing anonymisation reports in general and for an orphan drug in particular 27

Louise Martinsson

#### Policies 0070 and 0043: Juggling different requirements 31

Sybille M. Eibert

#### Clinical data publication by the EMA: The challenges facing the pharmaceutical industry 39

Wendelgard Pisternick-Ruf, Alexandra Marquart, and Thomas M. Schindler

#### Clinical trial results disclosure on ClinicalTrials.gov and EudraCT 44

Holly Hanson

#### Writing lay summaries: 49

#### What medical writers need to know

Namrata Singh and Vasudha

#### Lay titles for clinical trials: 55

#### A balancing act

Leonie H. E. Leithold, Clive M. Brown, and Thomas M. Schindler

#### Why clinical study reports really matter 59

Michael Köhler and Beate Wieseler

#### CORE Reference (Clarity and Openness 64

#### in reporting: E3-based) - a tool for modern clinical study reports in an era of increasing transparency and disclosure

Sam Hamilton and Debbie Jordan

#### Preparing clinical study reports for 68

#### external sharing - how to balance patient privacy/data utility priorities and manage risk

Cathal Gallagher

#### Harmonising format and style requirements for scientific and medical publications: Time to address a long-pending dream 71

Payal Bhardwaj and Raj Kumar Yadav

#### Special feature

#### Winners of the Geoff Hall Scholarship Essay Competition 80

#### Regular features

#### News from the EMA 76

- First-in-class medicine to prevent bleeding in haemophilia A patients with inhibitors
- General Court confirms EMA approach to transparency
- First medicine to treat neonatal diabetes
- Revised guideline on clinical studies for Alzheimer's disease medicines
- New tracking tool for EMA's relocation to Amsterdam
- EMA recommends immediate suspension and recall of multiple sclerosis medicine Zinbryta
- Prostate cancer medicine Xofigo must not be used with Zytiga and prednisone/prednisolone

#### Profile 83

- An interview with Chris Winchester

#### Journal Watch 86

#### In the Bookstores 89

- *An Introduction to Pharmacovigilance (Second Edition)*

#### Good Writing Practice 91

- Paragraph order distraction

#### Medical Devices 93

- "Medical Devices and Technologies - Emerging Opportunities for Medical Communicators"

#### Getting Your Foot in the Door 95

- Paving the path towards medical writing

#### Out on Our Own 97

- Opening up the room
- Finding my way in the world of freelancing - *in vitro* medical devices

# Medical Writing

## Public Disclosure

A paradigm shift in clinical trial data reporting is occurring as data becomes increasingly publically accessible. The EMA was the first regulatory authority to publish clinical data included in marketing authorisation applications.<sup>1</sup> The US FDA,<sup>2</sup> Health Canada,<sup>3</sup> and other health authorities are expected to follow. The US FDA has initiated a pilot project to release summaries from clinical pivotal trials included in approved New Drug Applications and has recently released a redacted drug approval package.<sup>4</sup> How similar future processes will be across individual regulatory authorities remains unclear. As new processes and systems are put in place by the different health authorities, fulfilling all requirements for public disclosure of clinical data will become increasingly challenging. This issue tackles the topic of public disclosure of clinical trial data with a wealth of helpful articles.

**Kathy Thomas** introduces and describes public disclosure of clinical trial data, especially current obligations and requirements in the EU/EEA. As part of this, she compares EU Regulation No 536/2014 and Policy 0070 (the EMA policy on publication of clinical data for medicinal products for human use).

**Raquel Billiones** provides two key articles on public disclosure of clinical trial data. The first article, authored with **Achim Schneider**, provides a useful guide on how to register, navigate, and access documents on the EMA website. She also explains how to download documents and retrieve examples of redacted documents together with their accompanying anonymisation reports.

In Raquel's second article, she reviews published anonymisation reports. Anonymisation reports are required by EMA Policy 0070 and describe how the data has been de-identified and the risk of re-identification assessed. Raquel explains that although most reports assess the risk of re-identification qualitatively, an increasing number assess risk quantitatively. In a related article, **Louise Martinsson** then describes her experience prepar-



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ing an anonymisation report for an orphan drug. With this example, she illustrates a step-by-step approach for preparing a report using quantitative methods to assess the risk of re-identification, including how a numerical threshold should be selected.

**Sybille Eibert** shares her first-hand experience of preparing documents to meet different transparency requirements. She relays some of the challenges in meeting EMA Policies 0043 (the policy on access to documents issued in 2010) and 0070 (issued in 2014). As Sybille explains, although "both policies aim to enhance the transparency of the regulatory decision-making process", they approach the challenge very differently.

In this relatively new era of public disclosure of clinical data, new standard operating procedures, working procedures, and practices are being developed by pharmaceutical companies and clinical research organisations. **Wendelgard Pisternick-Ruf and colleagues** share their thoughts on EMA

Policy 0070-related processes and the need to incorporate them into standard operating procedures and working practices. They also outline a process for implementing Policy 0070 and explore the challenges in accomplishing this alongside "transparency requirements of other channels" including those of ClinicalTrials.gov.

**Holly Hanson** continues by highlighting the differences between the requirements for data disclosure on the ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials (EudraCT) databases. She explains that proper planning for the disclosure of clinical trial results must occur to ensure that a Sponsor complies with these legal obligations. In particular, special attention must be paid to preparing disclosure documents alongside clinical study reports. She also provides details of which trials need to be disclosed and how and when the results are posted to the respective websites.

As part of EU public disclosure requirements, clinical trial sponsors are required to provide a summary of trial results that can be understood by a layperson, also called a Plain Language Summary. **Namrata Singh** and **Vasudha** discuss the content and writing style of a Plain Language Summary and illustrates her findings and proposals with a published summary. In a

As new processes and systems are put in place by the different health authorities, fulfilling all requirements for public disclosure of clinical data will become increasingly challenging.

following article **Leonie Leithold and colleagues** discuss the importance of having a correct title for lay summaries. They examine the content, format, and structure needed for the lay title to remain useful in several document types including Plain Language Summaries.

Although the main focus of this issue is disclosure related regulatory documents, public disclosure can be thought of as a continuum that includes clinical trial data published in peer-reviewed journal articles. Many peer-reviewed journals require authors to “share their raw, unprocessed data with other scientists and/or state the availability of raw data in published articles.”<sup>5</sup> To this end, minimum standards for anonymising data published in journal articles have been proposed.<sup>5</sup> **Kathy Thomas** touches on the implications of the need to include “a datasharing statement” in accordance with the recently updated guidance issued by the International Committee of Medical Journal Editors.<sup>6</sup>

Public availability of clinical trial data allows independent researchers and other decision-makers to have complete access to all the data from a clinical trial and not just selected data published in a journal article. However, even with standards for data anonymisation, often the full set of data from a single clinical trial are not always published or made available. **Michael Köhler and Beate Wieseler** from the Institute for Quality and Efficiency in Health Care in Germany emphasise the need for full access to clinical study data via clinical study reports. The authors highlight and discuss the potential for publication bias when only selected data are made available. They point out that clinical study reports contain “all information” and because they follow ICH E3 guidance, they provide a “high quality of reporting.” They welcome public disclosure initiatives and explain that they are expected to deliver full transparency and an increased access to all clinical trial data.

To conform with EMA Policy 0070 requirements, companies have applied retrospective redaction techniques (i.e., masking) to clinical reports submitted as part of their marketing authorisation applications. For these legacy documents, a de-identification process is applied to redact information in the finalised clinical document. Redaction in this context has mainly been performed manually by medical writing teams. **Cathal Gallagher** explains why there is scope for employing other less labour-intensive techniques. These procedures take advantage of automated techniques, which Cathal explains, are designed to improve efficiency by utilising

artificial intelligence and machine learning. He also looks to the future and outlines practices for anonymising individual patient data whilst maintaining data utility.

## EMWA efforts in clinical trial data disclosure

EMWA created the Regulatory Public Disclosure (RPD) Special Interest Group (SIG) to help share information around this fast-moving specialist topic and develop best practice in regulatory disclosure activities. In the EMWA News section, **Tracy Farrow**, the RPD SIG co-chair, introduces and explains the importance of the group to EMWA members. She also details the objectives of the group, explains what activities have already been undertaken, describes the resources available to EMWA members on the EMWA website, and outlines the group’s future plans.

With the CORE Reference user manual, EMWA has also been at the forefront of the challenge of creating a proactive authoring approach that takes into account requirements for later public disclosure.<sup>7</sup> **Sam Hamilton and Debbie Jordan** explain how this valuable, open-access document provides relevant and up-to-date information for preparing clinical study reports, as well as suggesting useful approaches to writing clinical study reports that minimise the need for later redaction.

To help regulatory medical writers, including freelancers, keep abreast of the new requirements for data disclosure, EMWA now offers a series of related conference workshops. Full details are included in EPDP brochure.

Finally, given the importance of this area of regulatory writing to EMWA members, future editions of *Medical Writing* will feature a new section on Regulatory Public Disclosure in which the RPD SIG will continue to share best practice, encourage discussion, and keep our members informed of any relevant updates in this fast changing environment.

## A final note

Regulatory public disclosure is a new and fast-moving area of regulatory writing. As such, regulatory medical writers must stay well-informed about updated regulations and requirements. From the breadth of the public disclosure topics presented in this issue of *Medical Writing*, it is clear that one size does not fit all on this journey to increased transparency.

I hope you find this issue of *Medical Writing* useful and interesting. I would like to thank all authors for their valuable contributions to what

I consider a new and exciting sphere of regulatory medical writing. As your guest editor, I have enjoyed reading your articles on the many different topics associated with regulatory public disclosure.

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# President's Message

## Dear EMWA Members,

In my first President's message I would like to say how honoured I am to represent EMWA and how excited I feel about the tasks of my new role. I would like to thank Abe Shevack and the other Executive Committee members for their great support and collaboration over the last year, and to warmly welcome Barbara Grossman in her role as Vice President. In the last year I had the opportunity to fully appreciate how essential the support of our volunteers is to make EMWA the great organisation it is. Various new initiatives and new structures have been set up, with new subcommittees and a new special interest group, and will need further efforts and development. Dear EMWA members, your support is highly welcome! Whether new to medical writing or experienced, your suggestions on topics for training, your feedback on the conferences, and your active support are highly appreciated.

The Spring conference in Barcelona was, once again, a great success and offered a broad spectrum of events and educational opportunities for new and experienced medical writers, with an extended workshops programme, a symposium on the opportunities for medical writers in the up-to-date area of medical devices, and four half-day Expert Seminar Sessions (ESS) with eight seminars on medical journalism, pharmacovigilance, and regulatory topics, including the hot topic of the General Protection Data Regulation. The symposium and the ESS sessions had excellent speakers from the industry, regulatory bodies, and international societies. Due to the relocation activities related to Brexit, the European Medicines Agency could not send a representative to the Spring conference this year, but expressed its interest in resuming soon the good collaboration with EMWA. The Freelance Business Forum and the Internship Forum rounded up the conference with their good attendance and successful initiatives.

The planning for the next conferences has already begun and we have started identifying a few up-to-date topics that deserve deepening in the ESS seminars and symposia. Let us know which topics you would like to be addressed in future conferences, in order for EMWA to timely react to a quickly evolving regulatory environment. On one hand, this represents a valuable opportunity for tailored and advanced professional education. On the other hand, it strengthens EMWA's role as the association of reference for training and network, and increases

I plan to further explore how to retain and re-attract experienced writers and long-term members. They represent a valuable source of expertise in medical writing areas, but also of experience with EMWA's activities and achievements over time. Their active involvement in our activities would further enrich EMWA.

EMWA's presence in current discussions through ESS sessions and symposia, which establish a dialogue between medical writers and international matter experts.

One of the most recent initiatives at EMWA is the Ambassador Programme, aimed to raise public awareness about medical writing through synergies with universities and research institutions. The first lectures were well received and confirmed the potential of this initiative to further spread the word about the professional role of medical writers and about EMWA. We plan to keep a track of the Ambassador lectures and to coordinate future efforts. Beside this, we plan to further develop our contacts with other professional organisations through reciprocal promotion and collaborative opportunities, as it has been done for CORE, the Joint Position Statement, and the BELS exam.

During my term as President, I plan to further explore how to retain and re-attract experienced writers and long-term members. They represent a valuable source of expertise in medical writing areas, but also of experience with EMWA's activities and achievements over time. Their active involvement in our activities would further enrich EMWA.

We will be constantly exploring how to further promote our organisation, to intensify our presence in the social media, to reach potential new members, to enhance the quality of our conferences, and to improve the offer to our members. I look very much forward to contributing to EMWA's further growth in this year as President!

**Tiziana von Bruchhausen**  
President@emwa.org



## EMWA webinar programme update

One of the benefits of being an EMWA member is having access to the webinar programme.

In 2018, we are providing a new webinar almost every month of the year either in live or recorded formats.

Thanks to our wonderful speakers, this year we've had the following webinars:

- More medical writing tips by Amy Whereat
- Key EU medical device regulations by Raquel Billiones
- Pharmacovigilance Special Interest Group update by Tiziana Von Bruchhausen and Lisa Chamberlain James

Upcoming webinars are described below.

### How to organise and deliver a webinar yourself

June 28, 2018, at 14:00 CET

Carolina Rojido

Now that internet-based learning and working are commonplace it can be useful to know how a webinar is done. Most of you probably know how to deliver training or a presentation. The EMWA webinar team can support EMWA webinar speakers by providing all the technical support necessary. However, you might find yourself in a situation where you need to be speaker AND organizer, or may be asked if you have this skill. Carolina Rojido will tell you how to prepare and run an engaging webinar smoothly.

### Writing guidelines

July 17, 2018, at 14:00 to 15:00 CET

Andrea Rossi

The Consolidated Standards of Reporting Trials (CONSORT) statement, issued in 2001, was the first example of a comprehensive and structured guideline including practical examples and a clear explanation of how to use it to communicate the results of randomised clinical trials (RCTs). In addition to these, different guidelines and checklists to use for the results of observational and many other types of studies have been published. The structure of CONSORT and STROBE guidelines will be reviewed in this webinar, which is a brief introduction to writing guidelines.

### Why you shouldn't miss the next EMWA conference?

August – This webinar, also open for non-members, will be recorded and is scheduled to be uploaded August 28, 2018.

Carolina Rojido & Laura C. Collada Ali

EMWA conferences provide a medium for networking, active discussions, and extensive cost-effective professional training. It's also an opportunity to benefit from the experiences of other medical writers.

Hear Carolina Rojido's thoughts about her

### SECTION EDITOR



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first conference experience. Laura Collada Ali has attended several conferences; she will discuss why she thinks they are so worthwhile.

### EMWA's webinar series

EMWA's webinars can be accessed at <https://www.emwa.org/training/emwa-webinars-programme/>. Webinars may be recorded or presented live. For live webinars, you only need to register and then connect to our webinars platform on the webinar date at the above address. A recording will be available shortly after the event in the Archive section. Nevertheless, we advise you to participate to allow you to ask questions and contribute the discussion. For recorded webinars, we encourage you to send us any questions by the date indicated so that they can be answered. For further information about webinars contact [webinar@emwa.org](mailto:webinar@emwa.org).

We'd like to thank our volunteers Irene Farré, Ananya Malladi, and Paul Wafula for their help in the development of the programme. New volunteers are always welcome!

If you would like to experience being a webinar speaker, you only need to provide your slides and present, we will take care of everything else!

**Carolina Rojido**  
and **Laura Collada Ali**  
[webinar@emwa.org](mailto:webinar@emwa.org)

## ISMPP U webinar on the Joint Position Statement on the Role of Professional Medical Writers

The AMWA-EMWA-ISMPP Joint Position Statement (JPS) on the Role of Professional Medical Writers emphasizes the importance of professional medical writers in promoting the use of guidelines for reporting the results of biomedical research. Many reporting guidelines are available, and a compiled list and links to the individual guidelines are available at the EQUATOR Network website. (See also Andrea Rossi's webinar on "Writing guidelines", above.)

At this ISMPP U webinar, you will hear from Caroline Struthers (EQUATOR Educa-

tion and Training Manager, UK EQUATOR Centre) and Karen Woolley (JPS co-author) about the goal shared between the EQUATOR Network and the JPS, and you will gain practical tips on how you can help the EQUATOR Network and how the EQUATOR Network can help you.

This JPS webinar is a joint educational webinar of ISMPP, AMWA, and EMWA. It will have long-lasting career benefits for writers and managers of writers. At the end of this webinar, participants should be able to:

- Describe why the JPS encourages profes-

sional medical writers to be guideline champions

- Access reporting guidelines that can enhance accurate, transparent, and complete reporting ... for almost any type of health research study
  - Recall three practical tips that could enhance a writer's career, based on use of the JPS and the EQUATOR Network
- The webinar was held on May 30, 2018. A recording can be accessed at <http://login.icohere.com/ISMPP?pnnum=SMM61577>.

## Conference reporting

At the May conference in Barcelona, for the first time, we had EMWA members reporting on key sessions. The objective was to allow EMWA members to learn from their colleagues' experiences and insights and to provide an opportunity for members to practice their journalistic skills. We will be publishing their short articles in the September issue of *Medical Writing*.

If you are interested covering one or more sessions of an upcoming conference, please contact EMWA Head Office at [info@emwa.org](mailto:info@emwa.org), with "Conference reporting" in the subject line.

## Freelance Business Forum report now available

The sub-committee report of the highly successful Freelance Business Forum held at the recent 46th EMWA Barcelona is now available. An overview and photographs of the event are presented, summarising the outcomes of Freelance Business Forum table discussions and the guest speaker

presentation. The table discussions continue to provide valuable expert advice in numerous areas of medical writing, editing, and translation work, for both experienced and new freelancers.

The report can be accessed at <https://www.emwa.org/freelance/freelance-resource-centre/>.



**Save the date**  
**EMWA Conference**  
November 8–10, 2018

For more information:  
<https://www.emwa.org/conferences/future-conferences/>

# WARSAW



Photo by Jane Marshall



Photo by Laura Kehoe and Allison Kirsop

## Winners of the Barcelona conference photo competition

At the Barcelona EMWA conference, members were asked to submit photos that included their EMWA 25th anniversary badge for a competition. Photos could be sent by email or Twitter. Winners were selected by the Executive Committee and included Jane Marshall, Laura Kehoe, and Allison Kirsop. Thanks to everyone who participated!

# The Regulatory Public Disclosure Special Interest Group

## Who are we and what do we do?

The Regulatory Public Disclosure Special Interest Group (RPD SIG) was first conceived in December 2015 and is a group of EMWA members supporting other EMWA members. The RPD SIG objective is: “to provide a forum for the discussion and sharing of information, best practices and ideas with EMWA members,” as mentioned at the RPD SIG’s launch at the Munich conference in May 2016. The concept of creating SIGs was initiated by EMWA in 2015 with the creation of the first SIG covering pharmacovigilance. The RPD SIG took up the baton shortly afterwards.

Christopher Marshallsay and I jointly chair the RPD SIG and are supported by other eager volunteers – either as part of the committee or as part of the advisory panel, our “global due diligence network” – who support technical and regulatory questions for the SIG.

### Current RPD SIG members are:

- Christopher Marshallsay (RPD SIG Co-chair)
- Alison McIntosh (guest editor for this special edition of MEW)
- Holly Hanson
- James Visanji
- Kathy Thomas
- Rafah Alhity
- Sam Hamilton (CORE reference representation)
- Tracy Farrow (RPD SIG Co-chair and CORE Reference representation)

### Current additional RPD SIG advisory panel members are:

- Art Gertel (CORE Reference representation)
- René Allard

## Why have an EMWA SIG on regulatory public disclosure?

The focus by industry and the general public on improving transparency around the drug development process has driven the industry and regulators to develop ever-expanding process steps and regulations to ensure transparency needs are met. The idea of being able to share

clinical trial data across multiple trials for research organisations to expand and speed up the drug development process is a noble one that strives to get treatments to patients faster. It is, however, challenging to deliver meaningful data and documents for reuse while protecting individual clinical trial participants’ personal data according to globally variable data privacy laws. This, coupled with rapidly changing regulations, has resulted in a complex minefield to traverse when dealing with regulatory public disclosure. It is therefore logical to have a forum where professionals can work together to understand the implications of data sharing.

Medical writing is increasingly involved in all forms of regulatory public disclosure with its impact on the structure and content of standard regulatory documents. The expectation is that the range of regulatory documents affected will burgeon in the coming years and that public disclosure will create the need for new regulatory documents, such as layperson summaries, which medical writers will support.

Various EMWA members involved in the field of public disclosure have been learning the hard way how to navigate through the new regulations and wanted to share their understanding and have a forum in which they could seek the advice of other experts in this area of medical writing – including what they have learnt and the challenges they have faced and overcome. The RPD SIG is a perfect forum for like-minded medical writers working in the field to impart knowledge, trade experiences, and develop best practices on a platform where they can share it more widely with EMWA members.

## RPD SIG activities to date

So far, the RPD SIG’s committee members have delivered and supported many activities, such as creating the RPD SIG website, which can be accessed from within the EMWA members-only section of the EMWA website. The website includes useful resources including a glossary, key references, background reading and videos, and a question and answer section.

Last year the RPD SIG delivered a successful full-day symposium on regulatory public

disclosure at the Spring conference in Birmingham where various presenters, including Juan García Burgos from the European Medicines Agency, gave interesting updates on their experiences to date. As follow-ups at subsequent conferences, the RPD SIG has provided topic updates and continues to deliver workshops on the various aspects that affect RPD from foundation-level introductions to advanced levels on specific areas such as redaction and layperson summaries.

Our latest efforts have been realised with this issue of *Medical Writing* dedicated to the topic of regulatory public disclosure with several of the committee members and other volunteers devoting time to write articles. We are pleased to announce that future editions of *Medical Writing* will include a regular RPD section with Sam Hamilton as the RPD SIG section editor. Hence, upcoming issues of the journal will feature additional articles on public disclosure, which we hope will continue to interest EMWA members.

## What next for the RPD SIG?

We welcome your ideas about what would be useful, and we continue to explore areas that will be helpful for EMWA members. We would welcome new, interested volunteers to support the RPD SIG. This support can range from committee membership to simply using the website, asking your questions, sharing your own experiences or suggesting ideas for future initiatives and areas requiring expansion. If you are interested in supporting us, please reach out to any of the current committee members for further information.

**Tracy Farrow**  
RPD SIG Co-Chair  
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# Clinical trial disclosure and transparency:

## Regulation EU No. 536/2014 Public disclosure at the clinical trial level

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### Abstract

The initial requirements of clinical trial disclosure were to register a clinical trial to make it publicly accessible to patients and thereby making the enrolment into a clinical trial easier. In the meantime, the disclosure of clinical trials in public databases has progressed to a new level, encompassing not only registration of new trials but also the disclosure of summary results for completed clinical trials for *all* drugs investigated in clinical trials, irrespective of their marketing approval status. Further development currently being implemented is the sharing of de-identified/anonymised trial participant data sets, thereby enabling re-analysis.

The Regulation EU No. 536/2014 is an EU law that instructs trial sponsors on the organisational, reporting, and disclosure aspects of clinical trials. The content of Regulation EU No. 536/2014 is intertwined with other obligations relevant to clinical trial disclosure and transparency efforts. Overlaps of the Regulation EU No. 536/2014 to other pertinent laws, policies, or required practices are summarised in this article, and some practical examples are provided for stakeholders who are involved in the planning, evaluation, and preparation of documents relevant to clinical trials.



### Introduction

Clinical trial disclosure is an evolving topic, with almost daily published contributions worldwide. The initial goal some 20 years ago of requirements that clinical trials be registered in a publicly accessible database was to inform patients, relatives, and treating physicians that a clinical trial exists, thereby making the enrolment into a clinical trial easier. In the meantime, the registration of clinical trials in large public databases has progressed to a new stage, involving disclosure of summary results for completed clinical trials for *all* drugs investigated in clinical trials, *irrespective* of the drug's marketing approval status. Further development currently being implemented is the sharing of de-

identified/anonymised trial participant data sets, which would enable re-analysis by a wider community of researchers. Such additional analyses could potentially expand the insights into the safety or efficacy of the investigated product. Also, data from several trials could be pooled into a meta-analysis, thereby enriching the level of information available to inform medical and prescribing decisions that would otherwise be based on individual studies.<sup>1,2</sup>

Countries of the EU and of the European Economic Area (EEA: Iceland, Liechtenstein, and Norway) as well as the US are particularly active in advocating and enforcing clinical trial disclosure. Additionally, some 40 countries worldwide have further national disclosure

obligations; indeed, in some countries there is even more than one relevant registry or database that needs attention.

The aim of this article is to summarise the Regulation EU No. 536/2014, which is the updated EU law that instructs trial sponsors on the organisational, reporting, and disclosure aspects of clinical trials. Key requirements of the new regulation and practical examples are described, with emphasis placed on topics of frequent discussions and relevance to medical writing, as well as other stakeholders closely involved in planning, supervising, evaluating, and reporting on clinical trials performed in the EU or relevant to an EU marketing authorisation application (MAA).

The content of Regulation EU No. 536/2014 should not be seen in isolation from other obligations relevant to clinical trial disclosure and transparency.<sup>3,4</sup> For this reason, in some sections of this article, similarities or overlaps to other pertinent laws, policies, or required practices are mentioned.

## Current disclosure obligations and requirements in the EU/EEA

### Regulation vs Directive

In legal hierarchy, any EU *regulation* is directly applicable under European Commission (EC) law and automatically becomes part of national law of the 28 EU member states (and also the EEA states). Therefore, a regulation is likely to achieve the intended purpose of the law in a fast and harmonised way among all the EU/EEA member states. In contrast, a *directive* is not directly applicable under the EC law; EU member states are required to implement directives, but they choose the form and methods of how to do that at a national level. This can result in a protracted process that often leads to imbalanced interpretation and realization of the law among the EU/EEA member states.

### Regulation EU No. 536/2014

Regulation EU No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use was adopted on April 16, 2014<sup>5-7</sup> (the “Clinical Trials Regulation”), repealing the Directive 2001/20/EC from 2004.<sup>8</sup> Furthermore, Regulation EU No. 536/2014 fulfils most of the requirements previously set by the Paediatric

Regulation (EC) No. 1901/2006 from 2006<sup>9</sup> regarding clinical trials in paediatric subjects, conducted in the EU.

Although Regulation EU No. 536/2014 came into force in 2014, its provisions will not take effect before mid 2020. This delay is due to challenges concerning the single EU portal and database system and are caused by complex technical demands regarding clinical trials data entry, as well as storage and information flow between the EMA and EU/EEA member states. During the interim (while the portal and database are being developed, tested and validated), the applicable laws remain in force, i.e. the Clinical Trials Directive 2001/20/EC<sup>8</sup> and the Paediatric Regulation (EC) No. 1901/2006<sup>9</sup> (the relevant items of the Paediatric Regulation are Articles 41, 45, and 46, which specifically deal with situations that may occur for clinical trials involving children). The clinical trial portal and database represent the key instrument that will be used as a single entry point for the submission of data and information and maintenance of clinical trial applications and authorisations within the EU/EEA (allowing interaction and collaboration of the member states and the EC). Only data and information defined in the Regulation EU No. 536/2014 as being submitted via the portal and/or stored in the database shall be held in that database (Articles 80 and 81 of the Regulation).

Public disclosure of clinical trial information is just one of the many aspects that are addressed in Regulation EU No. 536/2014 (sometimes referred to as “the new EU Regulation”). Overall, the law consists of 19 chapters with 99 articles, describing a precise and detailed procedure for the submission, assessment, and evaluation of requests for authorisation of clinical trials by the Concerned Member States (Part I and Part II), safety reporting procedures during the trial, the protection of subjects, and informed consent.<sup>10</sup> Once the new EU Regulation is fully adopted and operational, most of the activities between the member states and the EMA (on behalf of the European Commission) will flow through the new EU portal and all documents will be housed in the new database (that is currently being developed and tested). The functional specifications for the newly established EU portal and EU database were summarised by EMA in an informative document.<sup>7</sup>

Regulation EU No. 536/2014 applies to all interventional clinical trials performed in the EU;



it does not apply to non-interventional studies or studies of medical devices (unless the devices are part of a clinical trial involving a medicinal product).

For pragmatic purposes, the terms *clinical trial* and *clinical study* are used interchangeably in this article. However, it is noteworthy that in Regulation EU No. 536/2014, the EU regulators have emphasised a distinction between the terms *clinical trials* (which are “interventional clinical studies”) and *clinical studies*.<sup>5,6</sup> In this context, the term *clinical study* represents a broader concept; a *clinical trial* is defined as a specific type of a *clinical study*. In practice, a *clinical trial* is



characterised by specific elements including the presence of:

- An investigational medicinal product
- An active human intervention in defining the treatment
- A subject treatment assignment that does not fall within the normal practice of health care
- Monitoring of subjects throughout the course of the trial

#### European Medicines Agency

Implementation of Regulation EU No. 536/2014 falls under the responsibility of the EMA, which also manages the EU portal and the European

Union Drug Regulating Authorities Clinical Trials (EudraCT) database – known as the EU Clinical Trials Register ([www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)), which is currently used to store information on clinical trials performed in the EU/EEA.

The current database (and also the future database) is available *only* to clinical trials performed in the EU/EEA (i.e., those that have a EudraCT number) or to trials associated with regulatory applications in the EU/EEA and need to be disclosed because they are part of the Paediatric Investigation Plan (PIP) – such as those trials performed outside of the EU/EEA, in the so-called “third countries”. Currently, the

EudraCT database contains registration details on about 32,600 clinical trials (status May 2018) and is the largest source of information in the world on paediatric clinical trials.

#### Registration, disclosure of summary results, and disclosure of other data and documents for clinical trials in the EU/EEA

As shown in Figure 1, there are currently three main aspects of clinical trial disclosure in the EU, represented by Regulation EU No. 536/2014 and being at a level of a clinical trial:

1. Registration of a new clinical trial
2. Disclosure of summary results for a completed clinical trial
3. Upload of data and documents relevant to a clinical trial

In this context, it is essential to understand that Regulation EU No. 536/2014 addresses the public disclosure of clinical information, including the registration of *all* interventional clinical trials and release of result summaries from clinical trials for *approved* as well as *not yet approved* medicinal products.<sup>5,6</sup> Furthermore, when a clinical trial authorisation is denied, the date of decision on the trial is also taken as the date of the end of the trial, for the purposes of application of the disclosure rules and the posting of relevant documents (such as study protocol, Investigator’s brochure, etc) that are explained below and summarised in Table 1.

Similar rules also apply in the US, where legally binding requirements have been adopted for disclosure of clinical trials that are applicable under the US law, FDAAA 801 of 2007, which was expanded by the final rule making in 2016, known as the Final Rule.<sup>11,12</sup>

#### Registration of a clinical trial in the EU/EEA

Registration of a clinical trial in a public database (currently the EudraCT database) is required by law in the EU/EEA. The submitted information consists of details that are based on the clinical study protocol and includes the studied indication, primary and secondary outcomes, inclusion and exclusion criteria, estimated number of trial participants, and estimated time of outcomes completion. As the study proceeds, relevant study and timeline updates must be made (Table 1); the dates and the details of the updated information are part of a version control trail and available to the public view.

In the EU, after submitting an application for authorisation to perform a clinical trial to the EMA, selected information fields about the trial are released *automatically* to the public view by

EMA representatives in the designated member state; currently the information can be found in the EudraCT database ([www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)). In contrast to the EU/EEA, for clinical trials covered by the law FDAAA 801/Final Rule, it is the responsibility of the study sponsor (or a third party, assigned by the sponsor) to register the trial on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

It is noteworthy that regulators in the US involved in the Final Rule of the FDAAA 801 law have declined to require lay summaries of the clinical trial results for the time being until further research is conducted to determine whether summaries can be reliably and consistently produced without being promotional or misleading.

#### Disclosure of clinical trial summary results in the EU/EEA

Under the EU law, disclosing summary results (or *posting of summary results*, as it is also known) in the EudraCT public database has been mandatory since July 21, 2014, for all clinical trials that are shown in the EU database. This applies to trials that include at least one site in the EU/EEA and to clinical trials conducted in “third countries” that are linked to the EU PIP (Table 3).

For an interventional clinical trial in *adults* completed *before* July 21, 2014, disclosure of results can be made using the synopsis of an ICH E3-conforming clinical study report, or a pre-specified data set of summary results (“full data set”), or both. For clinical trials in *adults* that were completed on or *after* July 21, 2014, the full data set must be posted in the EudraCT database.

The usual timeline for posting results of trials in *adults* is within 12 months from the *last patient last visit (LPLV)* completion date. Notably, for *all* paediatric trials, summary results posting must be performed as full data set within 6 months from the LPLV completion date. Sponsors should be aware that trials involving children are those that include at least one participant that is younger than 18 years of age. Even the unintended inclusion of a trial participant younger than 18 *may* turn the clinical trial into one covered by paediatric rules. The timelines and modalities for posting results in the EudraCT database are explained in a document provided by EMA<sup>13</sup> (Table 1).

An item that is often discussed by those involved in the interpretation of the new

regulation and preparing disclosure documents, concerns the scope of the results disclosed with respect to the primary and secondary endpoints. The Regulation EU No. 536/2014 (Appendix IV) contains the following statement: “*Information shall be provided for as many end points as defined in the protocol.*”<sup>5</sup> Therefore, it is expected that the clinical trial summary should include results of *all* primary and secondary endpoints defined in the study protocol and in the statistical analysis plan – *not* just the main or key endpoints as is sometimes assumed. Endpoints that are evaluated post-hoc, as exploratory analyses, or “other” are not expected to be disclosed; however, such endpoints may be disclosed and the appropriate entry fields are available in the database.

Another subtle item of the EU law involves the reporting of results from the *intermediate analysis* of a trial. According to Regulation EU No. 536/2014, when the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial and the respective results of the clinical trial are available, a summary of those intermediate results should be submitted to the EU database within 1 year of the intermediate data analysis date.<sup>5</sup>

Finally, unlike the general understanding that details of Phase 1 trials will not be in the public view, the Regulation EU No. 536/2014 does have a provision for publicly disclosing these documents. Indeed, this is expected to start when the new database becomes fully operational.

These considerations are examples that have implications on study planning, defining of endpoints in the clinical study protocol, evaluation frequency of the data during the course of the study, and preparation of the clinical study report(s).

Such requirements are similar to those adopted for clinical trial results disclosure through the Final Rule of the FDAAA 801 law in the US. It is noteworthy that under the US law, results reporting is based on the primary endpoint completion date and is expected within 12 months (adult and children studies), followed by the disclosure of the secondary endpoints as they are completed. Under the US law, all endpoints included in the statistical analysis plan are mandatory for disclosure, whereas those designated as “other” endpoints are not expected to be disclosed.<sup>11,12,14</sup> Nevertheless, voluntary disclosure of “other” endpoints or analyses (meta-analyses) is encouraged, and the entry

**Table 1. Clinical Trial Disclosure: Summary of the main requirements in EU/EEA Regulation EU No. 536/2014**

EU/EEA (Regulation EU No. 536/2014)<sup>5,6</sup>

**Register** and disclose all *interventional* clinical trials with EudraCT number. Trial registration is performed by the EMA (Member State), upon receiving the official request for authorisation of a clinical trial on a medicinal product for human use

**Applies to trials ongoing or started:**

- After May 2004 for trials in adults
- After May 2006 for trials in children

**Applies to trials in:**

- Children: Trial category 1, 2, 3<sup>[4][7]</sup>
- Adults: Trial category (1), 2, 3<sup>[4][5]</sup>

**Disclose summary results for:**

- Any tested medicinal product, regardless of the regulatory approval status

**Timelines for disclosure of summary results:**

- Trials in children within 6 months of LPLV<sup>[1]</sup>
- Trials in adults within 12 months of LPLV<sup>[1]</sup>

**Additional documents to disclose:**

- Lay person language summary<sup>[1][3]</sup>
- Study Protocol (*each* version and modification)<sup>[1]</sup>
- IMPD (Section S and E)<sup>[3][6]</sup>
- Investigator’s brochure<sup>[3]</sup>
- Subject information sheet<sup>[3]</sup>
- Clinical study report (redacted)<sup>[3]</sup>

EU=European Union; EEA=European Economic Area; IMPD=Investigational Medicinal Product Dossier; LPLV=Last patient last visit:

- [1] Completion date of clinical trial is defined as the date when the final subject was examined or received an intervention for the purposes of final collection of data, whether or not the clinical trial was completed according to the study protocol or was stopped prematurely.
- [2] Deferred disclosure of results and documents is possible. A conditional deferral of posting is possible for trials with adults but not with children.
- [3] Timing of publication of these documents varies, depending on the trial category.<sup>6</sup>
- [4] For definitions, see Table 2.
- [5] Currently, data on Phase 1 trials in adults (that are not part of a PIP) are not made public; this situation may change when the single portal and database become functional.
- [6] Structure the IMPD sections as modules that can be easily separated and sent for public posting at different timelines (IMPD section S=Safety, section E=Efficacy; section Q=Quality is *not* disclosed).
- [7] A paediatric trial is a trial that includes at least one participant < 18 years of age.

**Figure 1 Overview of Disclosure EU/EEA Regulations EU No. 536/2014<sup>5-7</sup>**

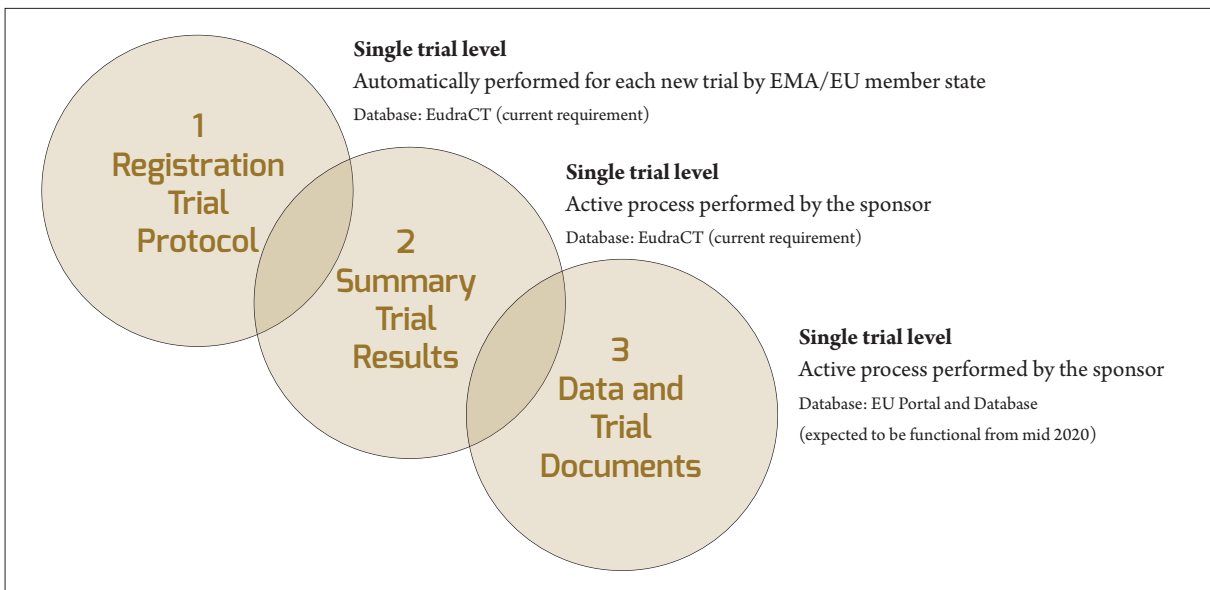


Table 2. Clinical trial disclosure EU/EEA: Supporting documents and definitions based on Regulation EU No. 536/2014

Document/Item	Content/Definition/Comment	Citation
Regulation EU No. 536/2014	Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014, on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.	5
Appendix, on disclosure rules, to the “Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014”	This document sets out rules and criteria for the application of the Regulation EU No. 536/2014.	6
Low-intervention clinical trial <sup>[1]</sup>	A clinical trial which fulfils <i>all</i> of the following conditions: <ul style="list-style-type: none"> <li>● The IMPs, excluding placebos, are authorised;</li> <li>● According to the protocol of the clinical trial, (i) the IMPs are used in accordance with the terms of the marketing authorisation; or (ii) the use of the IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the member states concerned; and</li> <li>● The additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any member state concerned.</li> </ul>	6
Category 1 trial <sup>[1]</sup>	Pharmaceutical development clinical trials include: <ul style="list-style-type: none"> <li>● Phase I clinical trials in healthy volunteers or patients; test whether a treatment is safe for people</li> <li>● Phase 0 trials – trials in healthy volunteers or patients; explore pharmacokinetics or pharmacodynamics</li> <li>● Bioequivalence and bioavailability trials</li> <li>● Similarity trials for biosimilar products</li> <li>● Equivalence trials</li> </ul>	6
Category 2 trial <sup>[1]</sup>	Therapeutic exploratory and confirmatory clinical trials include: <ul style="list-style-type: none"> <li>● Phase II and III trials</li> <li>● Not only trials by the MAH but also trials by other researchers looking at safety and efficacy in new indications, pharmaceutical forms and routes of administration, or patient populations and not covered by the definition of category 3.</li> </ul>	6
Category 3 trial <sup>[1]</sup>	Therapeutic use clinical trials include <ul style="list-style-type: none"> <li>● Phase IV clinical trials</li> <li>● Low-intervention clinical trial</li> </ul>	6

[1] Definition that applies for the purpose of Regulation EU No. 536/2014; IMP= Investigational medicinal product; MAH = Marketing authorisation holder

fields are available in the clinicaltrials.gov database.

**Disclosure of data and trial-relevant documents in the EU/EEA**

The third aspect of the Regulation EU No. 536/2014 shown in Figure 1 is related to the public disclosure of data and trial-relevant documents for *each* completed clinical trial; this aspect will become relevant when the new EU portal and database are active. Reports and other documents being placed into the public database should be redacted by the sponsor (or party

submitting the document or data to the database). It is the sponsor’s responsibility to redact/anonymise the documents before loading them into the system so that personal data (especially of clinical trial subjects) and commercially confidential information is not disclosed. A separate guidance is planned to be developed by the EMA regarding redaction/anonymisation of disclosed documents that fall under the Regulation EU No. 536/2014; it is expected that the scope of these processes will be consistent with that already available for EMA Policy 0070 (described later in this article).<sup>15,16</sup>

Based on the Regulation EU No. 536/2014, the documents that must be disclosed in an EU public database for each clinical trial are summarised in Table 3. The timelines for posting the various documents are not uniform; they depend on the category of the trial (i.e., category 1, 2, 3, as defined in Table 2) and on the age of trial participants.<sup>6</sup> By taking into account the development stage of the drug products, the regulators allowed a later disclosure of information for category 1 trials in comparison with category 3 trials. A general deferral of posting of these documents is possible for trials

with adults, but not for trials that have paediatric participants or for trials included in the PIP.<sup>6</sup>

Analogous requirements apply to clinical trials that are under the auspices of the FDA. The Final Rule of the FDAAA 801 law in the US mandates that the study protocol and statistical analysis plan (and *all* their amendments) be uploaded at the time of the summary results disclosure in the database [clinicaltrials.gov](http://clinicaltrials.gov) (usually 12 months after the completion of the *primary* endpoint of the study).<sup>11,12,14</sup>

### Plain language summary

The Clinical Trials Regulation EU No. 536/2014 (Article 37) requires sponsors to provide results summaries of clinical trials in a format understandable to laypersons (plain language summary), irrespective of the outcome of a clinical trial. Annex V of the Regulation EU No. 536/2014 lists 10 elements that must be addressed in summary of the results of the clinical trial for laypersons.<sup>5</sup>

When Regulation EU No. 536/2014 is fully adopted, the plain language summary must be provided by the sponsor as a separate document within 12 months of end of the clinical trial for each trial in category 2 and category 3. Thus, the plain language summary should be provided at the same time as the technical summary of trial results. Limited time deferral is possible, depending on the trial category and the disclosure option chosen by the sponsor.<sup>6</sup> A detailed guidance on how to prepare the plain language summary is available from EMA as well as from other health or clinical trial disclosure-relevant organisations and patient groups interested in this document.<sup>17,18</sup> The effort of preparing the plain language summary should not be underestimated. The challenges and experiences of preparing plain language summaries are described in a separate contribution in this issue of the journal. (See pages 49 – 54)

It is noteworthy that regulators in the US involved in the Final Rule of the FDAAA 801 law have declined to require lay summaries of the clinical trial results for the time being *until* further research is conducted to determine whether such summaries can be reliably and consistently produced without being promotional or misleading.<sup>11,12</sup>

### Transition period for Regulation EU No. 536/2014

As is common with new rules and regulations, a transition period will also apply to Regulation EU No. 536/2014.<sup>5</sup> Once the new regulation is fully adopted and the EU portal and database are functional, sponsors of clinical trials will have a 3-year transition period as follows:

**Year 1.** Trial can be submitted under either the new EU Regulation or the old EU Directive.

**Year 2 to 3.** Trial authorised under the old system remain under that system.

All new trials must be submitted under the new regulation.

**Year 4.** All ongoing trials running under the EU Directive must switch to Regulation EU No. 536/2014.

### Non-compliance

It is evident that throughout the world, information on numerous clinical trials eligible for registration and/or results disclosure is not fully disclosed. Nevertheless, until now no penalties have issued for non-compliance. In the EU and US, this may just represent a grace period to allow education and adjustment to the new legal requirements and to inform the regulated community of its obligations and ways of fulfilling them.<sup>12</sup> It is likely that this grace period is coming to an end.

In the EU, the importance of providing and maintaining public information is reinforced by Article 94 and 95 of the new regulation, which requires member states to develop penalties for failure to submit required information for public disclosure to the EU database.<sup>5,6</sup>

In the US, the Final Rule specifies civil or criminal proceedings and judicial consequences as well as monetary penalties (which could be calculated per day for each day of non-compliance if not corrected within 30 days after notice of non-compliance) and which affect not only the sponsor of a particular study but also the grantee institutions.<sup>11,12</sup>

### Regulation EU No. 536/ 2014 vs EMA Policy 0070

As described above, Regulation EU No. 536/2014<sup>5</sup> covers documents at the *single clinical trial* level (trials performed in the EU/EEA). Another disclosure requirement in the EU/EEA is EMA Policy 0070,<sup>15,16</sup> which deals with clinical trial documents and data at the *dossier level* (Figure 2).

EMA Policy 0070 has been in effect since January 1, 2015; it applies to the medicinal products whose marketing authorisation had been *approved* through a *centralised procedure* (... *and* also to those products for which marketing approval was *rejected* or *withdrawn*).<sup>15,16</sup> EMA Policy 0070 applies to “clinical reports” of studies that are beyond the scope of the Regulation EU No. 536/2014 (such as clinical trials that are conducted outside the EU but are submitted to EMA for marketing authorisation in Europe). The key characteristics of Regulation EU No. 536/2014 and EMA Policy 0070 are summarised in Table 3. Please note, that under EMA Policy 0070, the term “clinical reports” means several key regulatory documents of the Common Technical Document (CTD), submitted as part of the centralised marketing authorisation procedure, listed in Table 3.

In practical terms, this means that after submitting the dossier to the EMA for a marketing authorisation through a centralised procedure, clinical reports within the dossier are proactively released by the EMA into a dedicated clinical data database (<https://clinicaldata.ema.europa.eu>) soon after the decision on the marketing authorisation application has been reached. Documents in this database are available to the public either through an online application process or a contract agreement via “Terms of Use” between the applicant and trial sponsor. To prevent the release of personal data of clinical trial participants and certain commercially confidential information of trial sponsors, the documents anticipated for release into the database must first be redacted, de-identified, or anonymised by the sponsor – in conjunction with the EMA. This is a relatively new intense process that requires careful planning and organisation; this requirement should be taken into account early because it contributes to extra time and costs for sponsors when preparing and submitting documents for drug marketing authorisation through a centralised procedure.

### Implications of Regulation EU No. 536/2014

At the operational level, specific requirements of the new Regulation apply to the disclosure of information and documents. Although these requirements often differ only slightly from the usual reporting practices of a clinical trial, they do need to be planned by the trial managers and

Table 3. Summary of Regulation EU No. 536/2014 versus EMA Policy 0070

Item	Regulation EU No. 536/2014 <sup>5-7,13</sup>	EMA Policy 0070 <sup>15, 16</sup>
<b>Medicinal products covered</b>	Investigational medicinal products, irrespective of marketing authorisation status	Centrally authorised products only (approved products)
<b>Clinical trials covered</b>	Clinical trials conducted in the EU/EEA, non-paediatric trials included in a PIP, paediatric trials performed outside the EU/EEA that are included in a PIP, and paediatric trials involving an IMP covered by an EU marketing authorisation and sponsored by the MAH whether or not included in a PIP and whether performed in- or outside the EU/EEA (IMP=Investigational medicinal product; MAH=Marketing authorisation holder; PIP=Paediatric Investigation Plan)	Clinical trials submitted to the Agency in the context of a Marketing Authorisation Application, Article 58 procedure, line extension or new indication, regardless of where the study was conducted
<b>Documents disclosed</b>	Clinical trial-related information generated during the life cycle of a clinical trial, including the documents*:  Clinical study protocol, Assessment and decision on trial conduct, Summary of trial results including a Plain Language Summary/Lay Summary, Clinical Study Reports (main part), Inspections reports, Investigator’s Brochure, Investigational Medicinal Product Dossier sections S and section E, Subject information sheet. (IMPD section S=Safety and section E=Efficacy)	Clinical data (modules of Common Technical Document (CTD), including the following clinical reports and individual patient data*  CTD 2.5 Clinical overview, CTD 2.7 Clinical summaries, CTD 5 Clinical study reports main body of the report, Appendix 16.1.1 Protocol and Protocol amendments; Appendix 16.1.2 Sample case report form; Appendix 16.1.9 Statistical analysis plan), and the Anonymisation report that specifies and justifies the redactions and anonymisations indicated in the supplied documents.
<b>Disclosure channel</b>	EU Portal and EU Database Currently these are being developed, tested, and validated  During the interim time, the EudraCT database is used <a href="http://www.clinicaltrialsregister.eu">www.clinicaltrialsregister.eu</a>	EMA clinical data publication website <a href="https://clinicaldata.ema.europa.eu/web/cdp/home">https://clinicaldata.ema.europa.eu/web/cdp/home</a>
<b>Date when it applies</b>	Expected mid 2020	January 1, 2015 (new Marketing Authorisation Applications) or July 1, 2015 (Line extension or New indication)
<b>Disclosure</b>	Transition period of 3 years from the time of functional EU Portal, EU Database	Since October 2016

\*The disclosed documents need to be redacted/anonymised to protect trial participant personal data and sponsor-relevant commercially confidential information (CCI)<sup>16</sup>

Table is modified from a presentation by Ioana Ratescu, Legal aspects on transparency of clinical data – EMA perspective, 16Dec2016. Available at [https://ius.unibas.ch/fileadmin/user\\_upload/ius/11\\_Upload\\_Personenprofile/02\\_Assistenzprofessuren\\_oTT/Seitz\\_Claudia/Vergangene\\_Veranstaltungen/2016.12.16/Ratescu\\_Ioana\\_EU\\_Clinical\\_Trail\\_Regulation\\_Legal\\_aspects\\_on\\_transparency\\_of\\_clinicalvdata\\_-\\_EMA\\_Perspective\\_05.pdf](https://ius.unibas.ch/fileadmin/user_upload/ius/11_Upload_Personenprofile/02_Assistenzprofessuren_oTT/Seitz_Claudia/Vergangene_Veranstaltungen/2016.12.16/Ratescu_Ioana_EU_Clinical_Trail_Regulation_Legal_aspects_on_transparency_of_clinicalvdata_-_EMA_Perspective_05.pdf)

Figure 2. Regulations EU No. 536/2014 versus EMA Policy 0070<sup>5-7,15,16</sup>



Diagram is based on a presentation by Ioana Ratescu, Legal aspects on transparency of clinical data – EMA perspective, 16Dec2016. Available at: [https://ius.unibas.ch/fileadmin/user\\_upload/ius/11\\_Upload\\_Personenprofile/02\\_Assistenzprofessuren\\_oTT/Seitz\\_Claudia/Vergangene\\_Veranstaltungen/2016.12.16/Ratescu\\_Ioana\\_EU\\_Clinical\\_Trail\\_Regulation\\_Legal\\_aspects\\_on\\_transparency\\_of\\_clinical\\_data\\_-\\_EMA\\_Perspective\\_05.pdf](https://ius.unibas.ch/fileadmin/user_upload/ius/11_Upload_Personenprofile/02_Assistenzprofessuren_oTT/Seitz_Claudia/Vergangene_Veranstaltungen/2016.12.16/Ratescu_Ioana_EU_Clinical_Trail_Regulation_Legal_aspects_on_transparency_of_clinical_data_-_EMA_Perspective_05.pdf)



other stakeholders (medical writers, statisticians, and data managers) to ensure efficient information entry into the public database. Some requirements for the EudraCT database are summarised below:

#### Demography:

- Prepare a randomised trial participants list by **country** and by **pre-specified age categories** (for overall number of participants and for each treatment group)

#### Endpoints:

- Provide result information on **all primary endpoints** and **all secondary endpoints** that are pre-specified in the study protocol and in the statistical analysis plan. Statistical analysis of results is expected at least for the primary endpoints. If no statistical analysis is made for the primary endpoint, a “justification” is required by the database validation system. For such cases, have a brief justification statement ready.

#### Safety:

- Prepare *separate* tables for **non-serious adverse event** and **serious adverse events**; Show the number of trial participants affected by **non-serious adverse event** per treatment group (depending on the safety dictionary used, prepare outputs e.g. by System Organ Class, Preferred term).
- Show the number of occurrences for a particular adverse event (for overall and for each treatment group).  
A threshold can be applied (the threshold can be up to maximum 5% of participants affected by a particular adverse event in any treatment group).
- Show **all serious adverse events** (depending on the safety dictionary used, prepare an outputs e.g. by System Organ Class, Preferred term).  
Show the number of trial participants affected by a **serious adverse event**.  
Show the number of occurrences for a particular serious adverse event.  
Show relatedness to treatment.  
Show **all fatalities** and specify fatalities related to treatment.  
Some sponsors use a **customised file** for uploading the information on adverse events e.g. using a file in extensible markup language format (XML). Instructions for preparing an XML file for this purpose are available on the EMA Internet website (<https://eudract.ema.europa.eu/result.html> under Results related

documentation; EudraXML schemas and documentation).

## Publication of clinical trial results in peer-review journals

### Disclosure in public databases vs pre-publication considerations by peer-review journals

A frequently raised question by clinical trial sponsors and investigators is whether the disclosure of clinical results summary in a public database is considered to be a prepublication, possibly affecting a full publication of the trial results in a peer-review journal. A brief excerpt of the response by the International Committee of Medical Journal Editors (ICMJE) on this topic is shown below and is available in the section FAQs (Clinical Trials Registration) on the ICMJE website.<sup>19</sup>

*The ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. However, editors of journals that follow the ICMJE recommendations may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov (... or in other ICMJE-accepted public databases) to be prior publication. The ICMJE anticipates that the climate for reporting results for registered trials will change dramatically over coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results reporting.*<sup>19</sup>

### Implications of clinical trial results in the public database vs journal publications

The legally binding requirements on clinical trial disclosure in the EU/EEA are based on the Regulation EU No. 536/2014. The law includes public registration of a clinical trial and disclosure of summary results, all of which affects numerous regulatory documents relevant to a clinical trial. As such, the Regulation EU No. 536/2014 also affects other presentation of data in the public domain (professional conferences, publications in scientific and medical journals).

Demands for widened disclosure and transparency came from the recent “**data sharing**” policy released by the ICMJE. As such, trial sponsors are asked to indicate their readiness and willingness to share individual participant data in a “**data sharing statement**” when submitting a manuscript reporting a clinical trial for publication. This request is effective from July 1, 2018,

for manuscripts submitted to journals that follow the ICMJE recommendations. Furthermore, the ICMJE policy request that clinical trials that begin enrolling participants on or after January 1, 2019, must include a “**data sharing plan**” in the trial’s registration. If the data sharing plan changes after trial registration, the changes should be reflected in the statement submitted and published with the manuscript and also should be updated in the registry record.<sup>20</sup> The database [clinicaltrials.gov](http://clinicaltrials.gov) has the necessary fields already available for the “data sharing plan”, whereas in the EudraCT database these fields are not yet available but are in the planning stage.

## Final remarks

It is obvious that demands for disclosure and transparency information on clinical trial arise from numerous sources and stakeholder. Disclosure of clinical trial information is taken seriously by patients and physicians, pharmaceutical industry, journal editors, medical and scientific communities, private and public funders, regulators, politicians, and law makers.<sup>2,21-24</sup>

Publications of clinical trial results in professional journals is an important part of the disclosure endeavours and should be fully consistent with respective clinical study protocols, study reports, entries on company websites, and in public registries or databases. In the world of the internet, discrepancies can be easily identified between papers published in professional journals and information available in the other publicly accessible arenas.<sup>2,25-27</sup> Indeed, a trial tracker that shows sponsors’ compliance with disclosure of trial results is already available – at this stage only involving clinical trials registered in the [clinicaltrials.gov](http://clinicaltrials.gov) database (<http://opentrials.net/>);<sup>28</sup> nevertheless, similar efforts are underway to monitor compliance of sponsors for clinical trials located in the EudraCT database.

Clinical trials will continue to be performed in a global setting. The Regulation EU No. 536/2014 is just one of several instruments mandating compliance in transparency of public information. As such, national or regional laws and other efforts on disclosure and transparency will overlap and redundancies will be inevitable for some time to come. To be on the right path to achieve successful innovations in clinical research, clinical trial sponsors must adopt consistent, harmonised, vigilant, accountable, and transparent approach to the activities of clinical trials and information disclosure.<sup>29</sup>



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I am most thankful to my colleagues from both the Special Interest Groups on Clinical Trial Disclosure at the Drug Information Association (DIA) and from EMWA for sharing their knowledge during regular meetings and through personal interactions. Also, I am grateful to the staff members at the EMA and the NIH who are responsible for the respective public databases on clinical trial disclosure, for their professional updates on the topic and for clarifying the various requirements that are sometimes buried within the legal documents and technical elements of this important and fast-evolving topic.

## Conflicts of interest

The author declares no conflicts of interest.

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### Author information

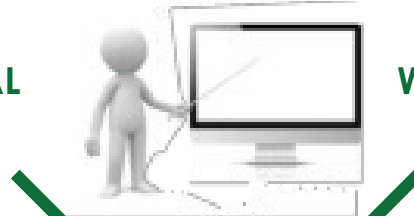
**Kathy B. Thomas, PhD**, is a fully independent freelance consultant who is based in Germany but works internationally. In addition to the typical medical writing activities and document preparation, she consults with sponsors of clinical trials on the current laws and regulations affecting clinical trial disclosure and also performs data entry (registration and results disclosure) in the respective databases.

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# Navigating the EMA clinical data website

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## Abstract

This paper describes how to register, access, and navigate the EMA clinical data website. One of the authors (RB) is a medical writer and accessed the site from the perspective of a pharmaceutical industry professional. The other author (AS) is not affiliated with this industry and accessed the website from the perspective of a lay person. Both authors reside outside of the European Union and were impacted by the role of geography in access rights and terms of use.

The authors present a step-by-step account of their experience in accessing and navigating through the EMA clinical database from a location outside of the European Union (EU).

## 1. Create an EMA account and log in

If you do not have an EMA account, you first

have to create one on the log in page of the website: <https://clinicaldata.ema.europa.eu/> (Figure 1).

Creation of an account requires completion of a self-service registration form, providing personal information and answering several security questions (Figure 2).

Once the form is completed, you will receive

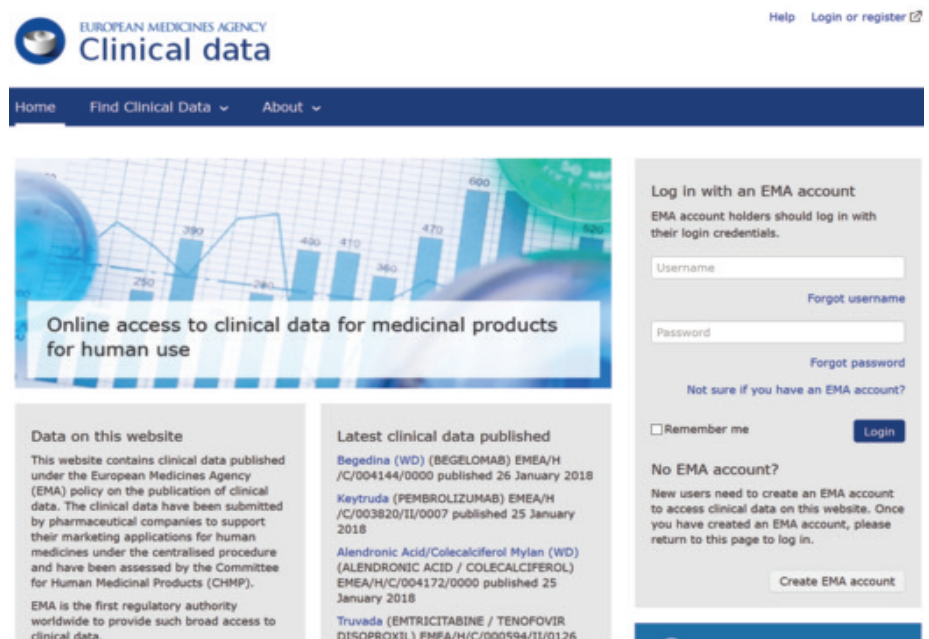


Figure 1. Log in page

**EMA - Self-service Registration Form**

Submit the following form to register.

**First Name \***  
Achim  
This is used to create your username and to address you in email correspondence.

**Last Name \***  
Schneider  
This is used to create your username and to address you in email correspondence.

**Email \***  
himder@acm.org  
We require a valid/active email address to create an EMA Account.

**Password \***  
\*\*\*\*\*  
Please enter a password that you want to use to access your EMA Account. The password must have at least 8 characters and must contain upper case, lower case, numeric and special characters.

**Confirm Password \***  
\*\*\*\*\*

**Mobile (optional)**  
  
This is an optional field. We will only use this information for security messages or alerts in relation to your account. Please include the international dialling code in front of your mobile number.

Figure 2. Self-registration form

**Personal Details**

Select country

First name \*  
Last name \*  
Address \*  
City \*  
Postal code \*  
Country \*  
Date of birth \*  
Passport or national ID Number \*

Country dropdown menu options: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Select country

Figure 3. Personal details needed for academic and other non-commercial research purposes

an email notification containing your registration information. With this information, you will be able to access the EMA clinical data website.

## 2. Access and terms of use

Choose the type of access you need. There are two categories of access to the data on this website, depending on the purpose. Each category has its corresponding terms of use. By accepting these terms, which you have to re-confirm each time you access the EMA site, you agree to be bound by these terms.

### (a) Access for general information purposes

This access type is for users accessing the published clinical data for general information

and other non-commercial purposes, including non-commercial research purposes. The user can only view the documents on screen. It does not allow the user to download, save, edit, photograph, print, distribute, or transfer any documents.

This type of access is available to everyone regardless of geographic location.

### (b) Access for academic and other non-commercial research purposes

This is for users accessing the published documents for the purpose of non-commercial research and academic use. More access rights are allowed under these terms of use, including downloading, saving and printing clinical reports, to be used solely for academic and other non-

commercial research purposes.

However, this access requires additional procedural steps and requirements. One of the requirements is to provide additional personal data, including date of birth, passport, or ID card number, and expiry date of the document. Another important requirement is provision of an address in the EU. The latter step cannot be circumvented because the pull down menu in the registration form only shows the 28 EU member states (Figure 3).

If you are residing outside of the EU, you can avail of the services of a third party resident of or domiciled in the EU. This third party shall be considered as the user for the purposes of these terms.

The authors are EU citizens but reside outside

Table 1a. Example of an export

Product Name	Active Substance	MAH	Product Status	Publication Date	Procedure Type	ATC Code
ILARIS	CANAKINUMAB	Novartis Europharm Ltd	Authorised	20/12/2017	Extension of indication	L04AC08
Zontivity	VORAPAXAR	Merck Sharp & Dohme Limited	Authorised	19/12/2017	Extension of indication	B01AC26
Trevicta	PALIPERIDONE	Janssen-Cilag International NV	Authorised	11/12/2017	Line Extension	N05AX13
Kyndrisa (WD)	DRISAPERSEN	BioMarin International Limited	Withdrawn	06/12/2017	Initial marketing authorisation	M09AX04

Table 1b. Further columns from export (product name column repeated for clarity)

Product Name	Generic	Bio-similar	Conditional Approval	Exceptional Circumstances	Orphan	Article 58 Procedure	Withdrawn Number	Procedure	No of Docs
ILARIS	No	No	No	No	No	No	No	EMEA/H/C/001109/II/0043	11
Zontivity	No	No	No	No	No	No	No	EMEA/H/C/002814/II/0005	18
Trevicta	No	No	No	No	No	No	No	EMEA/H/C/004066/X/0007/G	33
Kyndrisa (WD)	No	No	No	No	Yes	No	Yes	EMEA/H/C/003846/0000	105

Abbreviations: MAH, marketing authorisation holder

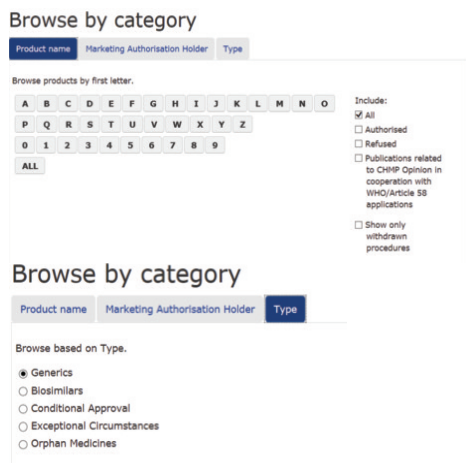


Figure 4. Browse search option

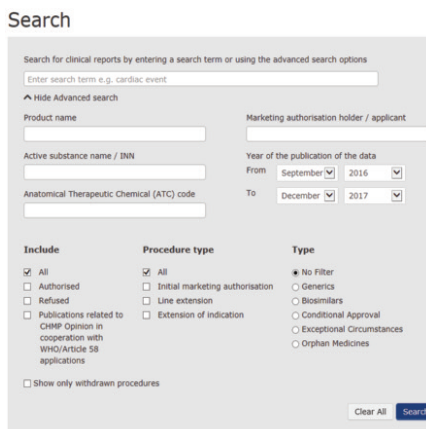


Figure 5. Advanced search option



Figure 6. Download page

of the EU and hence could only access the site through the first terms of use (“general information purposes”). However, one of the authors (RB) could upgrade her access rights to “academic and other non-commercial research purposes” after meeting the additional requirement of being able to provide a third party EU address. In this case, the third party was the affiliate of her company located in Germany.

### 3. Search options

Once granted access, you can search the site in two ways using the browse option or the advance option.

#### (a) Browse

You can browse by product name or by marketing authorisation holder name. Alternatively, you can browse by type of product or type of approval (Figure 4).

#### (b) Advanced search

The advanced search option entails entering search terms and applying additional filters such as date of publication and procedural type (Figure 5).

The search results can be downloaded as a table in \*.csv format. Such a file can be opened in a spreadsheet software such as Excel. An example of the search results export is shown below in Table 1.

### 4. Downloading documents

In order to download, you have to access each procedure individually. The reports are grouped into four categories: clinical overview, clinical

summary, clinical study reports, and anonymisation report. All documents within each procedure are searchable using text or keywords. The different documents under each category can be viewed by clicking on the “+” sign (Figure 6).

You can download the whole procedure or selected documents within a procedure. The documents are provided in \*.pdf format and are not hyperlinked.

### 5. Other features

On the clinical data website home page, there are several important tabs (Figure 7). The first tab provides details on the terms of use. The “how to” tab is a very helpful user’s tool and also provides additional information such as the most viewed clinical data to date.

The last two tabs are very important with respect to data protection. The “report patient re-identification” tab is part of the re-identification alert mechanism to ensure that the privacy of patients is protected.

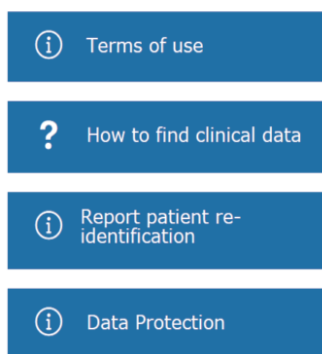


Figure 7. Other tabs to help users

The “data protection” tab is about protecting the rights of the registered user. It details how EMA collects, processes, and stores the data you provided during registration.

### Acknowledgements

All screenshots are used with permission from the EMA.

### Conflicts of interest

The authors declare no conflicts of interest.

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**Achim Schneider, PhD**, is a computer scientist with many years of corporate experience across various industries; he has a keen interest in applications of information technology to foster human development.

The authors are married to each other.



# Anonymisation reports from 2016 to 2017: A preliminary analysis

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## Abstract

The anonymisation report (AR) is a new and relatively unknown regulatory document, submitted as part of the redacted package of a marketing authorisation application under the EMA Policy 0070. The report documents the methodology of anonymisation in each package and the rationale for these methods. As of December 31, 2017, 64 ARs have been published on the clinical data website of the European Medicines Agency. A preliminary high-level analysis of these reports was performed, with the aim of gaining information on the current industry practices in anonymisation and AR preparation. After excluding 12 ARs from packages that did not contain protected personal data, 52 ARs were analysed. Information on anonymisation methodology, re-identification risk assessment, data utility assessment, and use of software is presented.

## Background

The EMA Policy 0070 (referred to henceforth as “the policy”) version 1.0 was finalised on March 2, 2016. At the time of writing, the policy has been revised three times, most recently (version 1.3) on September 20, 2017. As a

requirement of the policy, certain documents (“clinical reports”) in the marketing authorisation applications (MAA) are to be published on the clinical data website of the European Medicines Agency (EMA) (<https://clinicaldata.ema.europa.eu>). However, before these reports are published on a portal that is available to the general public, anonymisation of protected personal data and commercially confidential information, if applicable, is necessary. The resulting anonymised dossier that will be published is called the “redacted document package”; the first redacted packages were published on October 20, 2016. The policy provides guidance on the anonymisation process but “is not intended to mandate any specific methodology but to highlight to applicants/marketing authorisation holders (MAHs) the available techniques and those that EMA considers most relevant in the context of the anonymisation, to ensure that clinical reports submitted to EMA for publication are rendered anonymous prior to publication.”<sup>1</sup>

The “clinical reports” to be disclosed are documents (e.g., study reports, clinical summaries and overviews) that regulatory medical writers are very familiar with, except one. The anonymisation report (AR) is a new requirement under the policy and documents the methodology of anonymisation and assessment of re-identification risks in each package. Many companies are preparing the redacted packages and the AR for the first time and the industry is still gathering experience and know-how. The policy provides guidance on the structure and content of AR in Annex 1.2

Anonymisation Report – Template.

Approximately 14 months after the launch of the EMA clinical data website (October 2016 to December 2017), 64 redacted packages of marketing application procedures had been published, and each package contained an AR. This paper describes a high-level content analysis of these published ARs, with the purpose of gaining information on the current status and practices in anonymisation and the preparation of redacted packages as documented in the AR.

## Methods

The EMA clinical data website (<https://clinicaldata.ema.europa.eu>) was accessed under the academic and other non-commercial research purposes terms of use. Using the advance search option, all procedures of all types from September 2016 to December 2017 were retrieved (Figure 1) without the use of filters.

## Search

**Figure 1. Search method used to retrieve anonymisation reports from the EMA clinical website**

<https://clinicaldata.ema.europa.eu>  
Screenshot is used with permission from the EMA.





The search results were exported into an Excel file. Each package was accessed, with particular focus on the AR. Each AR was downloaded for further scrutiny. In addition to the package results obtained in the Excel export file, information on the content of the ARs was extracted, focusing on the following:

- Option used to establish effective anonymisation.
- Method of risk assessment of patient re-identification.
- Anonymisation approach.
- Data utility assessment.
- Use of software.

Additional analysis on orphan drug applications (ODA) was also conducted, as the risk for re-identification of subjects would appear to be higher in rare disease research and small populations.

This paper focuses on ARs only; the full redacted packages were not analysed. The methodology of this analysis was not validated but deemed sufficient to provide descriptive information about the ARs analysed. The analysis did not take into account potential overlaps among the ARs due to indication and line extensions of the same product.

All screenshots and publicly available information shown in this article are used with the permission of the EMA.

## All anonymisation reports from 2016 to 2017

A total of 64 redacted packages submitted by 29 MAHs were published from October 20, 2016, to December 31, 2017; 64 ARs in these packages were examined. Twelve packages did not contain any protected personal data; their ARs were excluded, leaving a total of 52 ARs for further analysis. The number of pages of these 52 ARs ranged from 4 to 53 pages. Figure 2 shows the individual AR, the month of publication, and other information.

A summary of information of anonymisation methodology in the 52 reports is provided in Table 1.

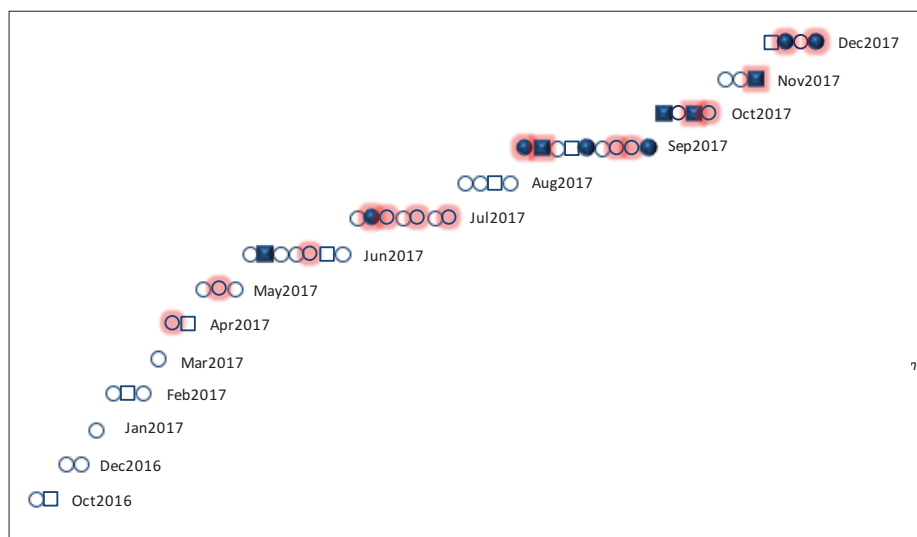


Figure 2. Anonymisation reports published on the EMA clinical data website from October 2016 to December 2017 (n=52)

Each symbol represents 1 AR.

Circles: ARs for non-orphan MAA (n=40)

Squares: ARs for MAA with orphan drug designation (n=12)

Filled symbols: ARs for MAA with quantitative risk assessment (n=11)

Symbols with red shadow: ARs for MAA that used automated redaction tools or artificial intelligence systems (n=16)

Table 1. Summary of methods described in anonymisation reports, October 2016 to December 2017

Information	All Reports N=52		Orphan Drug Application Reports N=12	
	n	%	n	%
<b>Demonstration of effective anonymisation</b>	<b>52</b>	<b>100%</b>	<b>12</b>	<b>100%</b>
Option 1: prevent singling out, linkage, inference	5	9.62%	2	16.67%
Option 2: re-identification risk assessment	45	86.54%	10	83.33%
Options 1 and 2 combined in 1 AR	2	3.85%	–	–
<b>Risk assessment of re-identification method</b>	<b>52</b>	<b>100%</b>	<b>12</b>	<b>100%</b>
Qualitative risk assessment (low, medium, high)	39	75.00%	6	50.00%
Quantitative risk assessment (numerical threshold)	8	15.38%	4	33.33%
Not applicable <sup>a</sup>	5	9.62%	2	16.67%
<b>Anonymisation method</b>	<b>52</b>	<b>100%</b>	<b>12</b>	<b>100%</b>
Non-analytical	32	61.54%	4	33.33%
Analytical	11	21.15%	5	41.67%
Not clearly specified	9	17.31%	3	25.00%

<sup>a</sup> All 5 ARs that used option 1



**Effective anonymisation**

The policy provides two options to establish effective anonymisation as described in Section 3.2.1 Anonymisation Criteria. The first option is to demonstrate that the anonymisation method used removes the possibility of singling out, linkage to, and inference to an individual patient. The second option is the evaluation of re-identification risk and demonstrating that the anonymisation method used mitigated this risk to the lowest level.

Only five ARs used the first option as shown in Table 1. An overwhelming majority (n=45; 86.54%) of ARs used the second option and assessed the risk of re-identification. For these ARs, the section on Fulfilment of the Criteria for Anonymisation was marked as “not applicable”. Two ARs by the same MAH used both options.

**Qualitative vs quantitative assessment method of re-identification risk**

The methods of assessing the risk of patient re-identification are presented in Table 1.

The five MAHs that used only effective anonymisation criteria option 1 did not perform re-identification risk assessment.

Of the 45 ARs that used effective anonymisation option 2, 39 (75%) assessed the risk of re-identification in a qualitative manner, using the scale of low, medium, or high risk. The scale is arbitrary and not detailed in the policy but most MAHs attempted to define this in their ARs.

Eleven ARs assessed the risk quantitatively, i.e., by calculating the probability of re-identification and measuring the risk numerically. The policy recommends a conservative threshold of 0.09 but allows for another threshold to be used as long as this is appropriately justified. There is a trend towards more frequent use of quantitative risk assessment towards the end of 2017 as shown in Figure 2.

**Analytical vs non-analytical anonymisation approach**

Most ARs (32 [61.54%]) described their anonymisation method as non-analytical, whereas 11 (21.15%) ARs claimed using the

**There is a trend towards the use of quantitative re-identification risk assessment and automated or artificial intelligence systems as the industry develops new tools and gains experience.**

analytical method of anonymisation (Table 1).

The terms “analytical” and “non-analytical” are not clearly defined in the policy and were used in the AR rather ambiguously, possibly coming from the policy’s Section 5.4 Anonymisation Process: “Applicants/MAH may not follow, in an initial phase, an *analytical approach*, and therefore it will not be necessary to calculate the risk of re-identification. In such cases *step 4* of the anonymisation process could be omitted.”<sup>1</sup>

Step 4 refers to the determination of quantitative risk of re-identification threshold. Hence, it is justifiable that many MAHs used the terms “non-analytical” and “qualitative” synonymously to refer to their anonymisation methodology. However, there are a few ARs that did not equate qualitative risk assessment with non-analytical approach, as demonstrated in this excerpt from one report: “Assessment of anonymisation has been performed using an *analytical approach* that evaluates criteria for anonymisation and expected risk factors on a *qualitative basis*.”<sup>2</sup>

Several MAHs described their “non-analytical” anonymisation approach as reviewing the documents manually and deciding on the text and numbers to be redacted based on predefined criteria. However, there were also ARs that used a “non-analytical” anonymisation approach using automated redaction tools.

All 11 ARs that used the quantitative risk assessment method also described performing anonymisation in an analytical manner. After anonymisation, the risks of re-identification were <0.09, the threshold suggested by the policy.

**Use of software**

Table 2 summarises the information on software mentioned in the ARs.

The use of some form of software was specified in 32 ARs, 16 of which referred to automated redaction tools or artificial intelligence systems (see Figure 2). Six ARs by two MAHs used the Lexicon Tool Suite by Privacy Analytics; 10 did not specify the proprietary name of the software used.

Sixteen ARs mentioned using manual redaction tools but only six specifically mentioned the proprietary name (Adobe Acrobat/Nuance). Twenty ARs did not mention the use of any kind of software.

The use of Lexicon Tools Suite allowed the

**Table 2. Summary of software use described in anonymisation reports, October 2016 to December 2017**

Information	All Reports N=52		Orphan Drug Application Reports N=12	
	n	%	n	%
ARs that do not mention the use of software	20	38.46%	4	33.33%
ARs that mention the use of software	32	61.54%	8	66.67%
ARs that used automated redaction tool/ artificial intelligence (AI) system	16	30.77%	3	25.00%
Lexicon Tool Suite	6	11.54%	3	25.00%
unspecified automated redaction tool/ AI system	10	19.23%	–	–
ARs that used manual redaction tool	16	30.77%	5	41.67%
Adobe Acrobat/Nuance	6	11.54%	1	8.33%
unspecified manual redaction tool	10	19.23%	4	33.33%



MAH to pseudonymise personal data by the use of transformation or recoding algorithms; redaction was only done where transformation was not possible.

Redaction of published patient data listings was performed in three procedures by one MAH that used Lexicon Tool Suite. It is to be noted that disclosure of patient listings is currently not obligatory, being out of scope in the phase 1 implementation of the policy. However, publication of listings is planned for phase 2 of the policy implementation.

#### Data utility considerations

The policy considers the impact of data transformations and redactions on the scientific utility of the report. In principle, a balance between an acceptably low risk of re-identification and maintainance of data utility should be achieved. The majority of ARs discussed data utility considerations descriptively. Only those ARs that used Lexicon Tool Suites ( $n=6$ ) described using metrics to assess data utility post-anonymisation. In these ARs, data utility was assessed by a) precision metric that measures data distortion following anonymisation b) subjective assessment criteria pertaining to the accuracy of analysis results based on the assumption that a secondary data user is planning to replicate the original results of the trial. Based on these metrics, data transformation combined with redaction resulted in higher data utility compared to a redaction-only approach.

#### Anonymisation reports for orphan drug applications

Of the 52 ARs analysed, 12 were from orphan drug applications (ODA) as summarised in Tables 1 and 2 and shown in Figure 2. These applications are of special interest as they deal with rare diseases and studies with small sample sizes. Six of the ODA ARs used the qualitative risk assessment method, four used the quantitative method, whereas two used the first option to establish effective anonymisation and hence did not perform any risk assessment. Five ODA ARs used the analytical approach of

anonymisation but only four performed quantitative risk assessment. Three ARs used the Lexicon Tool Suite for data transformation, automated redaction and data utility metrics.

The first AR that documented a quantitative measure of re-identification risk was that of an orphan drug, published in June 2017 (see Figure 2). The lessons learned from this redacted package are described in the article by Martinsson on page 27. There is no indication that ODAs are more likely to use the qualitative approach of risk assessment due to small study populations.

### General observations and recommendations

#### Analytical vs non-analytical approach to anonymisation

The terms “analytical” and “non-analytical” were frequently used in the ARs but rather ambiguously as described above. It is suggested that MAHs should provide clear definitions when using these terms in the ARs.

#### One-size-fits-all anonymisation methodology

Several ARs described one anonymisation methodology that appeared to apply to all studies in the package. While this may be true in some cases, this should not be the general practice. MAAs usually consist of trials of different phases and sample sizes and the level of re-identification risk may differ from study to study. It is suggested that ARs should be more specific about the methodology for each study.

#### Anonymisation of sensitive data

Not all ARs provided information on the anonymisation of sensitive data. Sensitive data are not easily identified, may be atypical data points and hence may be missed by automated tools. The policy does not define what data should be considered sensitive. Fortunately, the General Data Protection Regulation (GDPR 2016/679) rectifies this omission and defines sensitive subject data as “race or ethnic origin, political opinions, religion or beliefs, trade-union membership, genetic data, data concerning

health or sex life, or criminal convictions or related security measures.”<sup>3</sup>

It is recommended that ARs should define what data are considered as sensitive and how these data are identified and anonymised.

#### Pre- and post-anonymisation comparison

The policy requires that there should be no difference in terms of content between primary use reports and anonymised or redacted reports. Not all ARs published provided information on meeting this requirement. The AR should describe any technical changes (formatting, pagination, hyperlinks) that may have occurred as a consequence of the anonymisation process.

#### Data of deceased subjects

The policy refers to data protection of “natural persons”, thus excluding the deceased. Many trial subjects die during the course of a study as a consequence of underlying disease, yet their data are included in the report datasets.

Under the policy and the GDPR, these are no longer categorised as personal data. However, according to the Article 29 Data Protection Working Party, data on the deceased may be considered as personal information if they are linkable to living family members.<sup>4</sup>

The AR should specify how post-mortem data are dealt with during the anonymisation process.

### Conclusions

Anonymisation will rapidly evolve as technology continues to advance. The policy emphasises the importance of taking into account future developments when considering current anonymisation techniques. There is a trend towards the use of quantitative re-identification risk assessment and automated or artificial intelligence systems in anonymisation as the industry develops new tools and gains experience.

To the author’s knowledge, this paper provides the first analysis of ARs that have been published on the EMA clinical website. The site was found to be a very useful and user-friendly resource for this type of research. A guide to



navigating the site is provided in an article beginning on p. 17.

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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 by a clinical research organisation and may have been involved in the writing of clinical reports in the EMA clinical website.

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## The end of a successful pilot... GAPP retires after 6 years

The Global Alliance of Publication Professionals (GAPP) was set up in 2012 as a rapid response mechanism to counter misinformed or outdated articles about professional medical writing, publication planning and pharmaceutical industry sponsored publications. The original team incorporated individuals who served in leadership roles in the three main professional organisations – the American and European Medical Writers Associations (AMWA, EMWA) and the International Society for Medical Publication Professionals (ISMPP) – and who were located in different regions of the globe. Individuals have come and gone since the founding team, but we have always maintained that mix and geographic spread.

The conversation about industry funded research has been moving toward data disclosure and clinical trial transparency for some time. The volume of articles about industry sponsored medical publications has

decreased, and though misinformed or poorly researched articles are still being published, they have been focussing less and less on professional medical writing support. We responded to only four articles in 2017.

So, after 6 years and ~50 responses, the GAPP feels the organisation has served its purpose and the professional organisations have evolved to a point that we can hand back responsibility for rebuttals and responses to the respective governing bodies. We are confident that the professional organisations will act in concert to develop timely and influential responses that will serve to educate our colleagues and our critics. We are therefore announcing the retirement of GAPP, effective as of the close of the upcoming ISMPP meeting on May 2, 2018.

The GAPP website and response archive will be maintained, and the [contact@gappteam.org](mailto:contact@gappteam.org) email address will still be monitored for any member of our profession to report an article

they think justifies a response.

The retiring GAPP team would like to thank previous GAPP members as well as those who have referred articles to us over the years, and urges people to continue to be vigilant for inaccurate, misinformed, or outdated articles about our profession.

**Jackie Marchington**, Caudex, a McCann Health Company, Oxford, UK; ISMPP Advocacy & Outreach Committee co-Chair  
**Cindy Hamilton**, USA; Past AMWA President and Founding Member of GAPP  
**Art Gertel**, Principal, MedSciCom, LLC, Lebanon, USA; Past AMWA President and Founding Member of GAPP  
**Serina Stretton**, Proscribe, part of the Envision Pharma Group, Macquarie Park, Australia  
**Julia Donnelly**, Julia Donnelly Solutions, Derbyshire, UK; Past EMWA President.  
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# Preparing anonymisation reports in general and for an orphan drug in particular

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## Abstract

In 2015, the EMA Policy 0070 came into effect as part of EMA's commitment to increased data transparency. In short, clinical reports included in regulatory applications for example, marketing authorisations are published on the EMA web page and thereby made publicly available. Before the clinical reports can be published, the applicant is required by legislation to protect personal data to ensure individual clinical study participants and other individuals involved in the study are not identified. The applicant has to describe how data protection of personal data has been ensured in an anonymisation report (AnR). This article describes the different steps necessary to prepare an AnR in general, a company's first experience of preparing an AnR for an orphan drug, and the key points learned from this experience.

EMA Policy 0070 (the Policy) came into effect in 2016.<sup>1</sup> The Policy is part of an EMA initiative to increase transparency of clinical data and applies to three regulatory procedures in the framework of the centralised procedure. Since many of the terms in the Policy are unfamiliar to many medical writers, a list of terms and definitions used in this article is included in Table 1.

The clinical reports included in, for example, marketing authorisation applications are made publicly available under the Policy on the EMA webpage.<sup>2</sup> As part of any application under the Policy, two new documents are required; a table on justifications of commercially confidential information (not covered by this article), and an anonymisation report (AnR). A preliminary analysis on practices of AnRs published up to December 31, 2017, is provided in an article by Billiones on page 22 in this issue of *Medical Writing*.<sup>3</sup>



Table 1. Terms and definitions

Anonymisation	The process of rendering data into a form that does not identify individuals and where identification is not likely to take place
Anonymised/de-identified data	Data in a form that does not identify individuals and where identification through its combination with other data is not likely to take place
Data	Data in the context of the Policy means characteristics or information, usually numerical, that are collected through observation. The word can also be used to describe statistics (i.e., aggregations or transformations of raw data).
De-identification	See anonymisation.
Direct identifiers	E.g., patient ID, patient name, patient address
Clinical reports	Clinical reports in the context of the Policy means the clinical overviews (submitted in module 2.5), clinical summaries (submitted in module 2.7), and the clinical study reports (submitted in module 5, “CSR”) together with the following appendices to the CSRs: 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report form), and 16.1.9 (documentation of statistical methods)
Masking	An anonymisation technique in which data-identification data are irreversibly blocked
Personal data	“Personal data” shall mean any information relating to an identified or identifiable natural person (“data subject”); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.
Redaction package	The package contains the anonymised clinical reports included in the regulatory procedure under the Policy as well as some other documents defined in the Policy. A proposed redaction package is submitted first while the final redaction package is submitted after EMA’s review.
Publishing	The act of making data publicly available
Re-identification	The process of analysing data or combining it with other data with the result that individuals become identifiable, sometimes also referred to as “de-anonymisation”
Re-identification attack	An attack to identify an individual participating in a clinical trial. The reasons for attempting an attack could be, for example, to identify a trial participant of special interest such as a famous actor or a politician or to embarrass the data controller or to undermine the public support for release of data (demonstration attack).
Risk	The probability of re-identifying a trial participant.
Quasi identifiers	E.g., age, geographical location, sex, age, race, ethnicity

Since the applicant is responsible by legislation to protect personal data that can lead to identification of an individual, the applicant has to ensure these data are anonymised. The purpose with the AnR is to describe:

- The methodology of the anonymisation technique applied by the applicant.
- The rationale for the methodology used.
- How the risks of re-identification of the personal data have been measured and managed.

Two different anonymisation methodologies can be used, a quantitative or a qualitative one.

This article describes the procedures needed to prepare an AnR in general and is based on the EMA template for AnRs (Annex 1.2 in the Policy guidance).<sup>1</sup> Figure 1 presents a flow chart of activities included in the AnR preparation. In addition, the steps taken during the authoring of the first AnR based on a quantitative methodology published on the EMA webpage<sup>3</sup> are described and the key points learned from this experience are shared.

The AnR presented in this article was

prepared by Biogen, which was the marketing authorisation holder (MAH) for the medicinal product Alprolix® (indicated for the rare disease haemophilia B) in the United States, while Swedish Orphan Biovitrum AB (publ) (Sobi) as the MAH for Alprolix® in Europe, was responsible for submitting and revising the AnR after interactions with the EMA.

### Preparing the anonymisation report

The headings in this section of the article are derived from the Policy AnR template (Annex 1.2 Section 1.2.2.1.2 in the Policy guidance)<sup>1</sup> and are also used in Figure 1.

#### Anonymisation methodology

As a first step, the applicant should choose if a quantitative or a qualitative methodology should be used to anonymise personal data. The EMA encourages using a quantitative approach although they accept a qualitative approach during the pilot phase of the Policy implementation (Chapter 3, Section 5.4.4 in the Policy

guidance<sup>1</sup>). For the Alprolix® AnR, a quantitative methodology was chosen and the anonymisation technique masking was applied (Figure 2).

#### Recognising direct identifiers and quasi identifiers

As a second step, direct identifiers and quasi identifiers should be identified. This has to be done independently whether a qualitative or a quantitative methodology is used. The Policy guidance<sup>1</sup> provides examples of direct identifiers and quasi identifiers. If there are no direct identifiers and no quasi identifiers, a different EMA AnR template should be used (Annex 1.13, in the Policy guidance).<sup>1</sup>

The direct identifiers and quasi identifiers used in the risk assessment for the Alprolix® AnR are presented in Table 2. Since all patients were male and no deaths were reported during the trial, sex and date of death were not considered as quasi identifiers. In addition to the direct identifiers and quasi identifiers, some data were considered to be extra sensitive, i.e., HIV, hepatic C status, and genotype. These sensitive identifiers

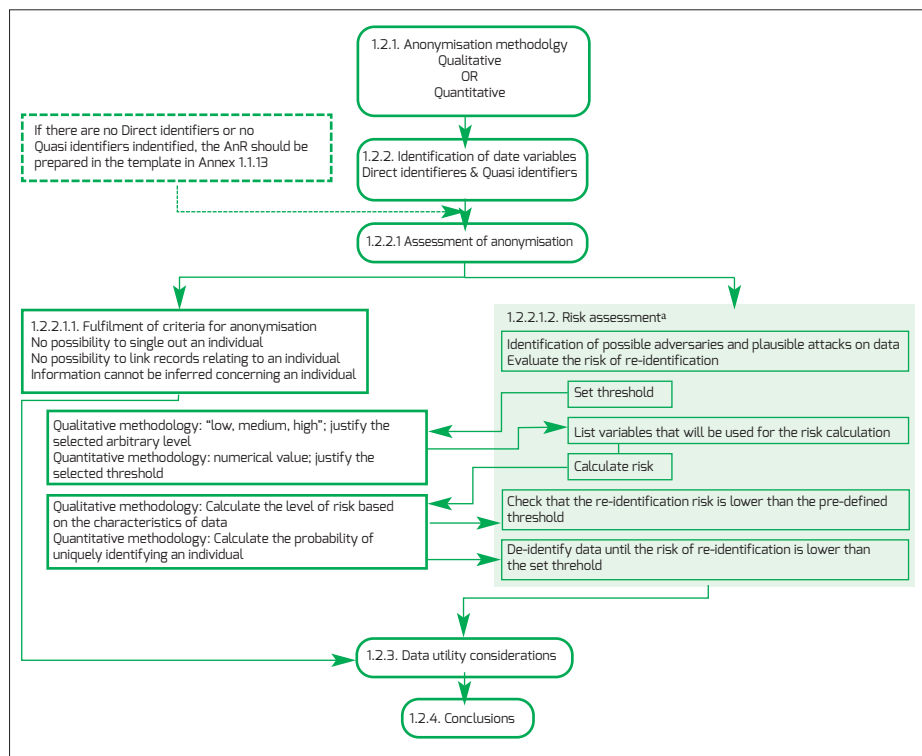


Figure 1. Flow chart of activities included in the preparation of anonymisation reports

\* Step 1.2.2.1.1 is not needed if a risk assessment (see step 1.2.2.1.2) is performed.

The numbers indicate the section numbers in the EMA anonymisation report template (Annex 1.2, in the EMA Policy 0070 guidance).

Table 2. Direct identifiers and quasi identifiers in the Alprolix anonymisation report

**Direct identifiers**

Subject identifiers
Study site identifiers

**Quasi identifiers**

Age, birthdate
Race
Ethnicity
Country
Height, weight, BMI
Serious adverse events;
Adverse events of Interest relevant to haemophilia B and/or treatment <sup>a,b</sup>
Medical history <sup>b</sup>
Surgery details
Bleeding episodes
Calendar dates

Abbreviations: BMI, Body mass index.

<sup>a</sup> Development of inhibitors, incidence of allergic reactions, incidence of thrombotic events, incidence of suspected transmission of an infectious agent, infection events, adverse bleeding events.

<sup>b</sup> Verbatim text and preferred term.

were masked in the clinical reports but were not part of the risk assessment of re-identification.

**Assessment of anonymisation**

As a third step, an assessment should be performed to assess the extent of anonymisation needed to reduce the risk of re-identification. If the applicant can confirm or demonstrate that the following three criteria are fulfilled, the EMA AnR template (Annex 1.2, Section 1.2.2.1.2 in the Policy guidance)<sup>1</sup> should not be completed:

- No possibility to single out an individual.
- No possibility to link records relating to an individual.
- No information can be inferred concerning an individual.

If one or more of the criteria are not met, the applicant should continue the assessment in the EMA AnR template (Annex 1.2 Section 1.2.2.1.2

in the Policy guidance).<sup>1</sup> For a qualitative methodology, there is no numerical threshold of risk of re-identification to be decided. Instead the applicant should use the arbitrary levels “low”, “medium”, and “high”. The following definitions are examples of levels to be used:

- High risk: < 100 trial participants, rare disease.
- Medium risk: 100 to 1,000 trial participants.
- Low risk: > 1,000 trial participants.

If a quantitative methodology is used, the risk of re-identification and a numerical threshold of risk of re-identification should be decided. The EMA recommends to set the risk of re-identification to a maximum, i.e., 1, and the numerical threshold of risk of re-identification to 0.09. However, the EMA leaves it open to the applicant “to decide on the most appropriate threshold for public disclosure of clinical reports” as long as a justification of the selected threshold is provided.<sup>1</sup>

The risk of re-identifying personal data in the Alprolix® AnR was based on the combined trial population in all clinical reports included in the marketing authorisation application. A number of scenarios and iterations combining different quasi identifiers were performed as presented in Table 3. In the scenario presented in the last row of the Table, there were no trial participants with a unique value for any of the selected quasi identifiers. The risk with this scenario was 0.006 (1/67).

**Data utility considerations**

As a fourth step, the applicant should consider the data utility versus the re-identification risk.

Since haemophilia B is a rare disease it was considered necessary to mask all quasi identifiers and the sensitive data on an individual participant level, including full narratives, to protect the confidentiality of the trial participants even though this reduced the data utility. However, since aggregate summaries and analyses have the most scientific value and remained largely unmodified, Sobi still considered the remaining data as informative. This was accepted by the EMA even though they do

Note: 1) Change in ABR, consumption and number of injections is calculated as onstudy value - prestudy value.  
 2) Subjects [redacted] were excluded from the analysis because their pre-study regimen was sports prophylaxis. Subject [redacted] had a pre- and on-study ABR but not pre- and on-study consumption and number of injections. Subjects [redacted] had pre- and on-study consumption and number of injections but not a pre- and on-study ABR.

Figure 2. Example of anonymisation by masking  
 The blue box covers personal data that needs to be anonymised.

**Table 3. Calculated risk for re-identification using different combinations of quasi identifiers in the Alprolix anonymisation report**

Redacted quasi identifiers	Unredacted quasi identifiers	Subjects	Number of unique subjects <sup>a</sup>	Proportion of unique subjects (%)
Height, weight, BMI	Age, race, country, SAEs, surgeries, bleeding episodes	167	149	89.2
SAEs, surgeries, bleeding episodes, height, weight, BMI	Age, race, country	167	124	74.3
Age, race, country, height, weight, BMI	SAEs, surgeries, bleeding episodes	167	53	31.7
Race, country, SAEs, surgeries, bleeding episodes, height, weight, BMI	Age	167	20	12.0
Age, race, country, SAEs, Surgeries, bleeding episodes, height, weight, BMI	–	167	0	0.0

Abbreviations: BMI, body mass index; SAE, serious adverse event.

<sup>a</sup>Number of subjects for whom the combination of values in the un-redacted identifiers is unique.

not accept this approach by default (Chapter 2, Section 2.2 in the Policy guidance).<sup>1</sup>

### Conclusion

As the fifth and final step, the applicant should declare that “the anonymisation report has been prepared following the guidance made available by EMA, and the anonymisation techniques have been applied consistently in the preparation of the documents comprising the Final Redacted Document package”.

### Key points learned from preparing an AnR

- Legal advice is important before choosing anonymisation methodology to ensure no data privacy laws are breached.
- If considering publishing personal data, have in mind that although a trial participant has consented to their data being published they have the right to withdraw their consent at any time.
- Statistical advice is crucial if a quantitative anonymisation methodology is chosen.
- Data anonymisation is a moving target as research, tools, and computational power evolve. Re-identification attacks (see Table 2) of anonymised data do occur and are becoming more common (Henriksen-Bulmer et al.).<sup>5</sup>
- Note that anonymisation of personal data in relation to trial participants (Chapter 3, Section 5.3)<sup>1</sup> differ from personal data in relation to investigators, sponsors, and applicants (Chapter 3, Section 6).<sup>1</sup>
- During the “implementation phase” of the Policy, the EMA offers advice (telephone conferences, face to face meetings, written conversation). This service is provided to all applicants when submitting their first AnR under the Policy. The author’s experience was that EMA was interested in discussing the problems encountered, as well as the applicant’s opinion of the Policy. The EMA also

provided valuable feedback on the AnR and assisted in improving the quality of the AnR.

- The timelines in the Policy guidance did not apply when this article was authored. Check with the EMA when to submit your proposal package.
- Be sure to use the most recent version of the Policy guidance as it is being updated frequently. EMA Questions & Answers<sup>6</sup> provide useful tips on how to interpret the Policy guidance.<sup>1</sup>
- EMA offers small and medium sized companies a redaction tool licence for 12 months. An application for the tool should be done five months prior the expected CHMP opinion.

### Concluding remarks

The preparation of the AnR is in its early stages and both the EMA and, in particular, applicants/MAHs have a steep learning curve ahead until the AnR can be considered a mainstream regulatory document. As the Policy, including the AnR, is still in the implementation phase and companies as well the EMA are still learning, the preparation of the Alprolix® AnR should only be consider as an example of how to prepare a quantitative AnR.

### Acknowledgements

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### Disclaimers

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

### Conflicts of interest

The author Louise Martinsson is employed by Sobi, a biopharmaceutical company with a focus on rare diseases.

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# Policies 0070 and 0043: Juggling different requirements

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## Abstract

EMA Policies 0043 and 0070 allow access to a broad range of regulatory documents. This article compares the two policies, highlighting key differences relevant for medical writers and professionals focussing on clinical data transparency. This article then summarises Teva's experience with implementing Policy 0070 and preparing the company's first two Policy 0070 dossiers for publication. Finally, the article reviews major challenges and how to overcome them, for example, how to consider previous Policy 0043 requests for the same drug product. Medical writers need to become familiar with these policies because the increased dissemination of regulatory documents will affect how these are prepared in the future.

Two policies of the EMA grant access to previously undisclosed regulatory clinical documents. In November 2010, the policy on access to documents (Policy 0043) was adopted.<sup>1</sup> This was followed in October 2014 by the policy on publication of clinical data (Policy 0070).<sup>2</sup> Both policies aim to enhance the transparency of the regulatory decision-making process. An additional objective of Policy 0070 is to allow the scientific community to apply the knowledge from past clinical development programmes to future research.

Although the objectives of the two policies are similar, their scope, approach, and procedures

differ (see Table 1 overleaf). According to phase 1 of Policy 0070, after a medicinal product has received a marketing authorisation, its regulatory clinical documents (clinical study reports [CSRs], clinical summaries, and clinical overviews) must be published on an EMA website. In contrast, Policy 0043 allows anyone to request a wide range of clinical and other documents from the EMA without giving a reason. In the vast majority of cases, EMA grants the request, and only the requester receives the documents.<sup>1-5</sup>

According to both policies, protected personal data (PPD) and commercially confidential information (CCI) must not be released in order to protect the privacy of individuals and the commercial interests of drug developers. Personal data is defined as "any information relating to an identified or identifiable natural person" in Regulation 45/2001, to which both policies refer.<sup>6</sup> Clinical documents typically contain personal data of study participants, such as participant identification numbers. Clinical documents may also contain personal data of staff from sponsor, investigational sites, and vendors, such as phone numbers. CCI is defined

in Policy 0070 as "any information ... that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant". Policy 0043 has a similar definition of CCI. The EMA Questions and Answers document for Policy 0070 further confirms that there "will be no difference in the understanding of CCI in the Agency's assessment" between both policies.<sup>1,2,7</sup>

Currently, redacting or masking (rendering information invisible with a coloured bar) is the most widespread method to protect personal data under Policy 0070. Other anonymisation techniques to protect personal data, such as randomisation and generalisation, are encouraged by EMA for Policy 0070.<sup>8</sup> For Policy 0043, redaction is the only accepted method to prevent release of PPD, since it ensures compliance with the legal requirement to grant access to the original documents. For CCI, redaction is the only possibility for preventing release according to either policy.<sup>6,8-11</sup>

Between October 2016, when the clinical data publication website for Policy 0070 went live, and December 2017, EMA published documents for 64 product dossiers. However, by



Table 1. Key differences between Policies 0070 and 0043

Characteristic	Policy 0070 <sup>a</sup>	Policy 0043
Regulatory basis	No direct legal basis <sup>b</sup> ; complementary tool before Clinical Trial Regulation 536/2014 comes into force	Direct legal basis: Regulation 45/2001
Effective date	January 1, 2015	December 1, 2010
Access to documents	Proactive publication on EMA website with options to view and download	Reactive: based on a specific request and released to the requester only
Scope	Clinical CTD Module 2 and 5 documents from concerned dossiers submitted via centralised marketing authorisation procedure (for CSRs: body/synopsis, protocol/amendments, CRE, statistical analysis methods)	In principle, any documents about medicinal products for human and veterinary use held by EMA
Availability of documents	<i>Per Policy:</i> Published within 60 days after EC decision <i>As long as EMA has a backlog:</i> Much later, e.g., more than 1 year after EC decision	After finalisation of regulatory procedure (e.g., after EC decision) <sup>c</sup>
Trigger for MAH to initiate work	<i>Per Policy:</i> MAH can proactively prepare redaction proposal versions <i>As long as EMA has a backlog:</i> MAH may choose to wait for EMA notification letter (not advisable for a large dossier)	EMA receives a specific request for document(s) and consults MAH
Deadline for requesting redactions	<i>Per Policy:</i> Submission of redaction proposal package within 30 days before and 10 days after CHMP opinion <i>As long as EMA has a backlog:</i> Deadline for redaction proposal package per notification letter from EMA, usually several months after letter <sup>d</sup>	MAH usually has five working days to comment on a (batch of) document(s) sent by EMA
Anonymisation report required?	Yes	No
Who provides initial suggestion for PPD anonymisation and how?	MAH (as read-through redaction marks)	EMA (as highlights)
Who decides on PPD anonymisation?	MAH (in consultation with EMA)	EMA (after consultation of MAH)
Amount of PPD anonymised	Usually more than for Policy 0043 <sup>e</sup>	Very limited <sup>e</sup>
Method to protect personal data	Redaction or other anonymisation methods	Redaction only
Who carries out anonymisation/redactions for PPD and CCI?	MAH	EMA
Appearance of redaction marks	PPD: blue box with black overlay text; CCI: black box with red overlay text	Black boxes without overlay text for both PPD and CCI

## Abbreviations:

CCI, commercially confidential information;  
 CHMP, Committee for Medicinal Products for Human Use;  
 CRE, case report form;  
 CSR, clinical study report;  
 CTD, common technical document;  
 EC, European Commission;  
 MAH, marketing authorisation holder;  
 PPD, protected personal data.

<sup>a</sup> Timelines for the redaction proposal package and the publication step apply to initial MAAs, line extension applications, and extensions of indication applications. For Article 58 applications and withdrawals, see External Guidance.<sup>8</sup>

<sup>b</sup> See Questions and Answers document for Policy 0070.<sup>7</sup>

<sup>c</sup> For details and exceptions by document type, see.<sup>3</sup>

<sup>d</sup> For the first dossiers, MAHs were granted only about 2 to 3 months' time from EMA notification to redaction proposal document package.<sup>27</sup> More recently, the timeframe is longer, e.g., up to about 6 months; see<sup>13,14</sup> and Table 2.

<sup>e</sup> Based on Teva experience, the published dossiers on the clinical data publication website,<sup>12</sup> and.<sup>21</sup>

**Table 2. Characteristics of the first Teva dossiers subject to Policy 0070**

Characteristic	Dossier A	Dossier B
Type of product and application	Initial MAA for a monoclonal antibody	Initial MAA for a combination product: two generic substances plus a device
Clinical studies	Six Phase 3, four Phase 2, and four Phase 1 studies	Four Phase 1 studies
Clinical documents	30 documents	9 documents
Total page count for clinical documents	Approximately 29,000 pages	Approximately 2,500 pages
Special considerations	Includes several old “legacy” documents without text recognition; includes CSRs based on several different templates and thus with different structure	Two duplicate submissions (different tradenames with identical sets of clinical documents) requiring one redaction proposal document package but two final redacted document packages
Date of positive opinion	June 2016	June 2016
Date of EMA notification	May 2017	July 2017
Due date of redaction proposal document package	Early August 2017 Following a request for deferral, a revised due date in early September 2017 was granted by EMA	Early November 2017
Publication date	April 2018	February 2018

Abbreviations: CSR, clinical study report; MAA, marketing authorisation application.

December 2017, a total of 337 product dossiers were subject to publication under the policy. This backlog means that the timelines defined in the policy are not currently applicable. Instead, the EMA notifies marketing authorisation holders long after the Committee for Medicinal Products for Human Use (CHMP) issues an opinion for a product. EMA grants marketing authorisation holders up to about 6 months from notification to the due date of the redaction proposal document package.<sup>12–14</sup>

The following sections of this article describe the implementation of Policy 0070 at Teva (for branded medicinal products) and some of the challenges we had while preparing our first two dossiers subject to Policy 0070. The focus is on Teva-internal processes rather than the procedural steps outlined in the EMA guidance.

## Implementing Policy 0070

To provide direction on practical aspects of Policy 0070, EMA published a guidance document (the so-called External Guidance) in March 2016 and a related Questions and Answers document in March 2017.<sup>8,15</sup> To date, the External Guidance has been revised three times, most recently in September 2017. The revisions were issued while preparation of the

two Teva dossiers was ongoing. It was therefore essential for Teva to continuously follow any changes in EMA’s requirements. Uncertainties in interpretation of the guidance were clarified through interaction with EMA (via industry associations’ webinars and direct interaction, especially for the first dossier with pilot phase) and in discussion with our vendor and other companies (via industry associations).

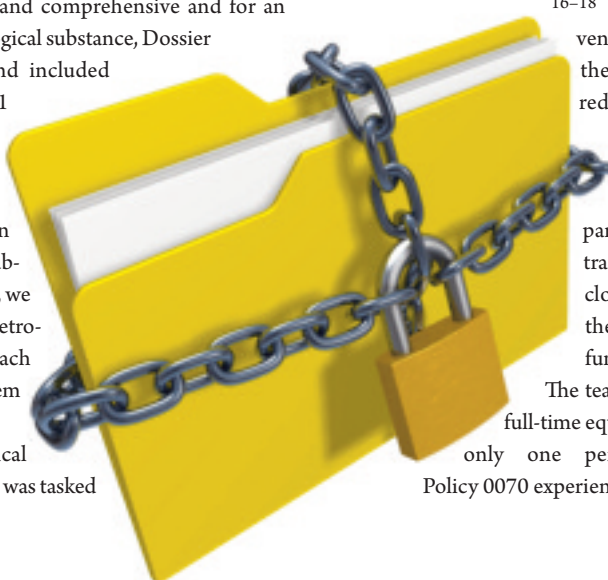
The two dossiers that this article covers were quite different and thus serve well to illustrate various challenges. While Dossier A was relatively large and comprehensive and for an innovative biological substance, Dossier B was small and included only four phase 1 studies (see Table 2). Since all documents had been written without their publication in mind, we had to follow a retrospective approach to preparing them for publication.

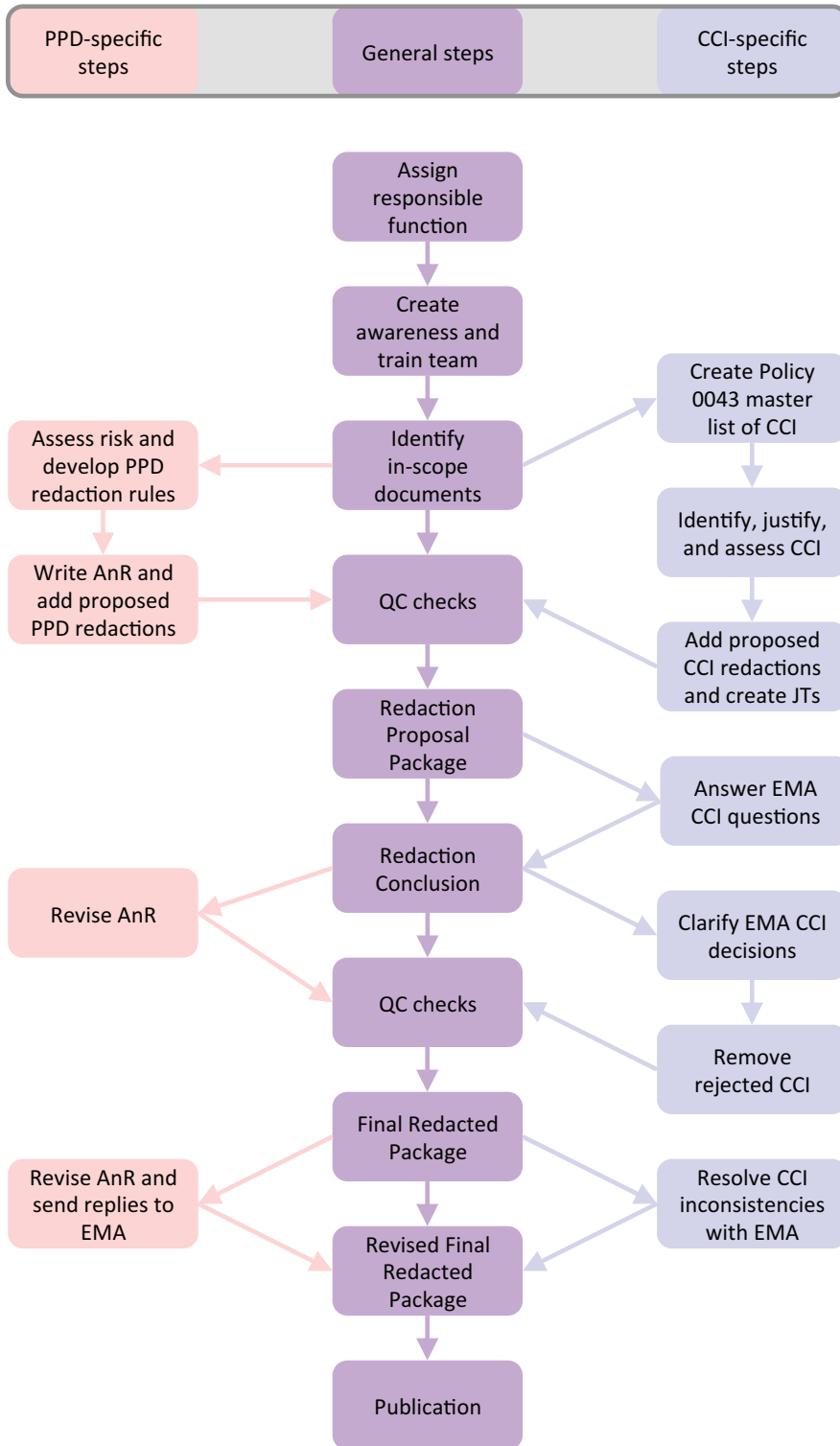
The medical writing function was tasked

to lead Policy 0070 preparations at Teva well before the expected CHMP opinions for the first concerned dossiers. A medical writing vendor with Policy 0070 experience and a software tool to search for PPD was engaged (see Figure 1). Next, a Teva medical writing representative set out together with the vendor to create awareness of Policy 0070 among a broad cross-functional group of Teva stakeholders. Over the following months, the Teva medical writing representative and vendor developed a set of draft PPD redaction rules based on published guidance.<sup>8</sup>

<sup>16–18</sup> Thereafter, the vendor started with the proposed PPD redactions for the Dossier A documents in scope of Policy 0070. In parallel, a dedicated transparency and disclosure team within the medical writing function was formed.

The team comprised four full-time equivalents, of whom only one person had prior Policy 0070 experience.





**Figure 1. Important process steps for preparing a public dossier according to Policy 0070.**

Steps apply to Dossier A, although most steps were also relevant for Dossier B. PPD-specific steps are shown on the left, CCI-specific steps on the right. Common and general steps are presented in the middle column. Abbreviations: AnR, anonymisation report; CCI, commercially confidential information; JT, justification table; PPD, protected personal data; QC, quality control.

By the time we received notification from the EMA for Dossier A, draft PPD redaction proposal versions of the clinical documents and a draft anonymisation report summarising and justifying the PPD redaction approach had almost been completed. However, the identification of potential CCI had not yet begun. Since no internal procedural guidance was available, the transparency and disclosure team prepared ad hoc process plans, guidance documents, and quality control checklists. It took the entire workforce of the transparency and disclosure team to deliver the redaction proposal package for Dossier A on time, while substantially less in-house resources were required for the small Dossier B.

### Protecting personal data

Maintaining data privacy and minimising the risk for an individual to be re-identified are important pre-requisites for clinical documents to be made public. Thus, the marketing authorisation holder must anonymise the clinical documents before publication. At the same time, “a maximum of scientifically useful information” should be retained to ensure data utility for secondary research. However, protecting the privacy of clinical study participants and maintaining data utility are competing objectives because methods that increase data privacy often reduce data utility.<sup>8</sup>

Teva decided to redact PPD in Dossiers A and B based on a qualitative, non-analytical assessment of the risk of re-identification. This is similar to most of the first dossiers published per Policy 0070.<sup>12,13,19,20</sup> A fairly conservative PPD approach was chosen to achieve a very low risk of re-identification. This was justified by the permanent public release of the documents and likely better technological means to re-identify individuals in the future. In addition, more and more personal data may become publicly available over time. This may facilitate linking

data from Policy 0070 documents with other public data to re-identify individuals. For these reasons and because access to documents via Policy 0043 is not public, considerably more PPD was redacted in Teva’s first Policy 0070 dossiers than what EMA usually accepts for Policy 0043 requests.<sup>21</sup>

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PPD-related internal steps including finalisation of the PPD redaction rules, the PPD redaction proposals, and the anonymisation reports were carried out by the transparency and disclosure team in consultation with a legal expert for data protection and a regulatory affairs representative, involving colleagues from clinical development, pharmacovigilance compliance, and statistics as needed.

The anonymisation report is not formally adopted by EMA, and the anonymisation approach is the responsibility of the marketing authorisation holder.<sup>8</sup> Nevertheless, we received a number of detailed EMA comments on the anonymisation reports during the pilot phase for Dossier A and as part of the redaction conclusions for both dossiers. Most importantly, EMA insisted on the anonymisation reports being dossier-specific and listing only those personal identifiers that actually occur in the dossier. The implementation of this comment was a time-consuming challenge because it had not been built into the PPD redaction process and required an additional search of all documents. Furthermore, not all EMA feedback for the anonymisation reports was consistent across both dossiers. Although not an expectation per the current guidance,<sup>8</sup> EMA requested replies to their comments and further modifications of the anonymisation reports after submission of the final redacted document packages (see Figure 1). Thus, our experience substantiates EMA's announcement at the industry associations' webinar in January 2018 to focus more on quality and specificity of anonymisation reports in 2018.<sup>13</sup>

## Identifying commercially confidential information

EMA states in Policy 0070 that in general “clinical data cannot be considered CCI”. What may be accepted as CCI is a matter of considerable debate and remains a case-by-case assessment, particularly given the “lack of a legal definition” of CCI.<sup>1</sup> According to recent decisions of the EU General Court for three Policy 0043 cases, marketing authorisation holders need to provide “concrete evidence of how the release of the contested documents would undermine their commercial interests”.<sup>22</sup> After 1 year of Policy 0070 clinical data publication, proposed CCI was rejected in 76% of the instances. The most frequent reasons for rejections were insufficient justifications followed by information being available in the public domain.<sup>13</sup>

For Dossier A, subject-matter experts from clinical development/pharmacology, intellectual property, bio-assays/immunology, chemistry/manufacturing/control, regulatory affairs, statistics, and non-clinical development were consulted to identify potential CCI. Up front, the transparency and disclosure team educated the subject-matter experts on what might be CCI according to these criteria: 1) information is covered in Annex 3 of Policy 0070, and 2) the item is not listed in Chapter 4 of the External Guidance as information not considered to be CCI, and 3) the item does not meet any of the five EMA rejection codes. In addition, for each CCI item, the subject-matter experts were requested to provide “a specific, pertinent, relevant, not overstated, and appropriate justification” explaining how the release of the information would damage the company's commercial interest.<sup>8</sup>

For Dossier A, subject-matter experts were asked to highlight suggested CCI in the PDF documents and add justifications within the PDF highlights. The transparency

and disclosure team then worked with the subject-matter experts to verify which items were not public, to shorten lengthy CCI suggestions to succinct and specific items such as a word or a number, and to improve the justifications. Quality control checks throughout and across documents aimed to mark CCI items in a consistent manner. As a final and time-consuming step, the transparency and disclosure team together with the vendor created the CCI justification tables and transformed the PDF highlights into correctly formatted CCI redaction proposals (see Figure 1).

For Dossier B, a modified process for identifying CCI was tested. Subject-matter experts were asked to add suggested CCI plus justification to a single justification table for the entire dossier. Checks to verify the suggested CCI items were performed based on this master justification table. Thereafter, the remaining CCI item was marked for redaction in the PDF. This process was much more

manageable than the process for Dossier A. However, since Dossier B was small with few suggested CCI items, the acid test will be Teva's next large dossier with an innovative medicinal product.

A major challenge, in particular for the preparation of Dossier A, were previous and parallel requests for documents for the same product according to Policy 0043. Even if a document in scope of Policy 0070 has previously been released according to Policy 0043, the marketing authorisation holder still has to prepare a new version of the same document for Policy 0070 publication. This is because different methods are required to mark or highlight items for redaction (refer to Table 1); thus, a new version has to be prepared even if the same items were redacted for both policies. In addition, earlier CCI decisions for documents requested according to Policy 0043 but not in scope of Policy 0070 may be relevant for preparing the Policy 0070 dossier, if the respective content is also found in any documents in scope of Policy 0070.

To prevent CCI redactions rejected under

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Policy 0043 from being included within the Policy 0070 redaction proposal package, a master list of items that were accepted or rejected per Policy 0043 was created as a reference source. However, EMA decisions for one relevant Policy 0043 request were obtained too late to allow appropriate consideration for all applicable documents in the Policy 0070 redaction proposal package. This and further aspects (e.g., the large number of scanned pages, and the number and complexity of CCI items suggested by the subject-matter experts) prevented full consistency of proposed CCI across documentation at the time of the Policy 0070 redaction proposal package. Furthermore, EMA decisions on the acceptability of CCI were not consistent between both policies. Hence, additional discussions with EMA and CCI modifications were required after the redaction conclusion and following submission of the final redacted document package (refer to Figure 1).

According to the External Guidance, we expected to have a CCI redaction consultation with a chance to clarify or elaborate on certain CCI justifications. However, apart from a request for further information for two CCI suggestions, EMA proceeded straight to the redaction conclusion.

In general, many proposed CCI redactions were rejected, mainly because justifications were not considered sufficient, the information was in the public domain, or information was considered to be common knowledge. Nevertheless, in the majority of the 30 Dossier A documents, certain CCI items (many occurring more than once) were accepted. Most of the accepted items concerned manufacturing details and immunological bioassay specifications.

## Outlook and role of medical writers

EMA's two transparency policies are the first but not the only initiatives to grant widespread access to regulatory clinical documents. Further initiatives by the EMA,<sup>23</sup> the US FDA,<sup>24,25</sup> and Health Canada,<sup>26</sup> are already effective or are planned to start soon. Although consistency across these initiatives would be highly desirable, new challenges in preparing documents to meet different transparency requirements are expected.

Even if medical writers are not directly involved in preparing documents for release or publication, they need to be aware of the fate of the documents they write. Anticipating the subsequent publication, medical writers can help facilitate the redaction process by adjusting the content and structure of clinical documents. Medical writers can reorganise and streamline company templates for CSRs, clinical study protocols, and statistical analysis plans so that PPD and CCI are minimised upfront, limited to fewer locations within a document, and more easily identified for anonymisation and redaction. Furthermore, medical writers can advise which content is necessary per CSR and Common Technical Document guidelines so as not to compromise the primary purpose of the original documents to support regulatory approval. Medical writers may also help prepare anonymised versions of documents, when a company starts employing PPD anonymisation methods other than redaction. Finally, medical writers are experts in targeting regulatory documents to various audiences, which now also include the general public.

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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 by Teva Pharmaceuticals International GmbH.

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# Clinical data publication by the EMA: The challenges facing the pharmaceutical industry

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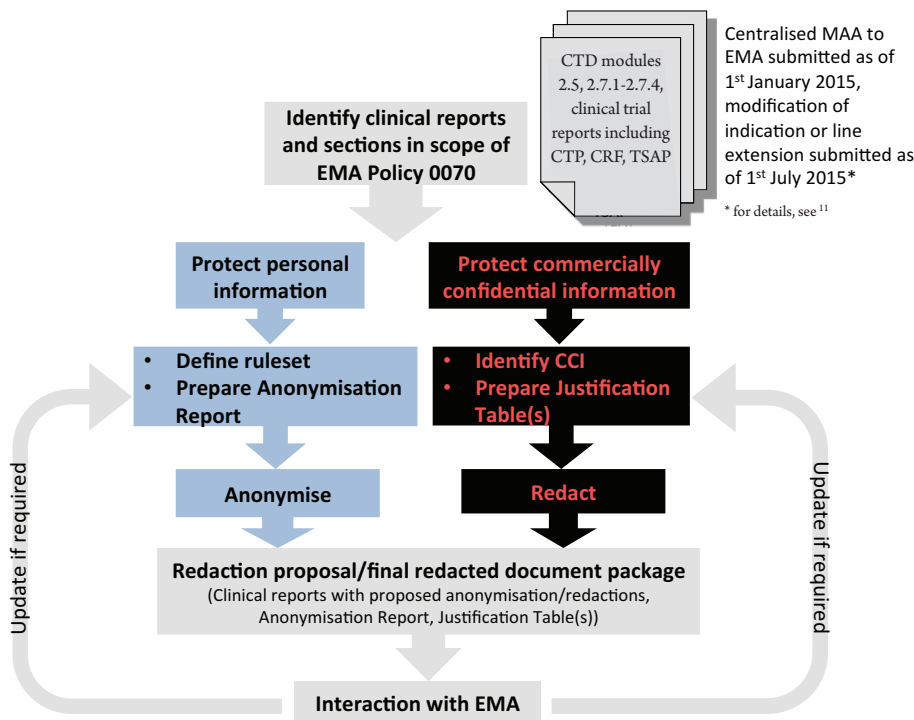
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## Abstract

As of October 2016, EMA publishes clinical data on their clinical data website (<https://clinicaldata.ema.europa.eu>). This new procedure applies to all marketing authorisation applications submitted by pharmaceutical companies under the centralised procedure to the EMA. Before publication of the documents in scope, companies have to ensure that personal data of trial participants and personnel as well as commercially confidential information is protected. This article describes the challenges for sponsors to implement and maintain efficient and up-to-date processes that also take into account the multitude of transparency requirements of other channels, such as ClinicalTrials.gov.

## Introduction

Globally, more and more health authorities are establishing regulations to enhance clinical data transparency. Sharing of clinical information is being recognised as beneficial to medical progress; it enhances trust in the authorities' decision-making processes, enables academics and researchers to re-assess the data, and allows healthcare professionals and patients to make more fully informed decisions.<sup>1,2</sup> The European Medicines Agency policy on publication of clinical data for medicinal products for human use, also known as EMA Policy 0070, became effective in January 2015,<sup>3</sup> and its website (<https://clinicaldata.ema.europa.eu>) went live in October 2016. Other regulatory agencies, such as Health Canada, follow the European approach and also propose the release of clinical information on drugs after the regulatory review process has been completed.<sup>4</sup> Similarly, the US FDA have just started a pilot programme to evaluate the potential benefit of disclosing key



**Figure 1. Main sponsor tasks in preparing a document package for publication on EMA's Policy 0070 website**

Abbreviations: CCI, commercially confidential information; CRE, case report form; CTD, Common Technical Document; CTP, clinical trial protocol; MAA, marketing authorisation application; TSAP, trial statistical analysis plan.

information included in pivotal clinical trial reports.<sup>5</sup>

All these transparency initiatives have in common that their regulations impose additional and differing obligations with regard to scope, format, and timelines on sponsors. To be compliant, companies need to establish internal processes and increase their capacity to meet the evolving requirements. Whilst the intention of more transparency is acknowledged and supported by the pharmaceutical industry,<sup>6,7</sup> the first year of experience with EMA Policy 0070<sup>8</sup> shows that less than a fifth of all users of this information were registered for academic and other non-commercial research purposes. This is in line with experience from EMA Policy 0043,<sup>9</sup> where more than half of the document requests came from the pharmaceutical industry and law firms.<sup>10</sup>

## EMA Policy 0070

The core of EMA Policy 0070 Phase I is the publication of clinical reports after conclusion of the regulatory decision-making process within the centralised marketing authorisation procedure.<sup>11</sup> Thus, the policy applies to marketing authorisation applications for medicinal products derived from biotechnology processes, orphan

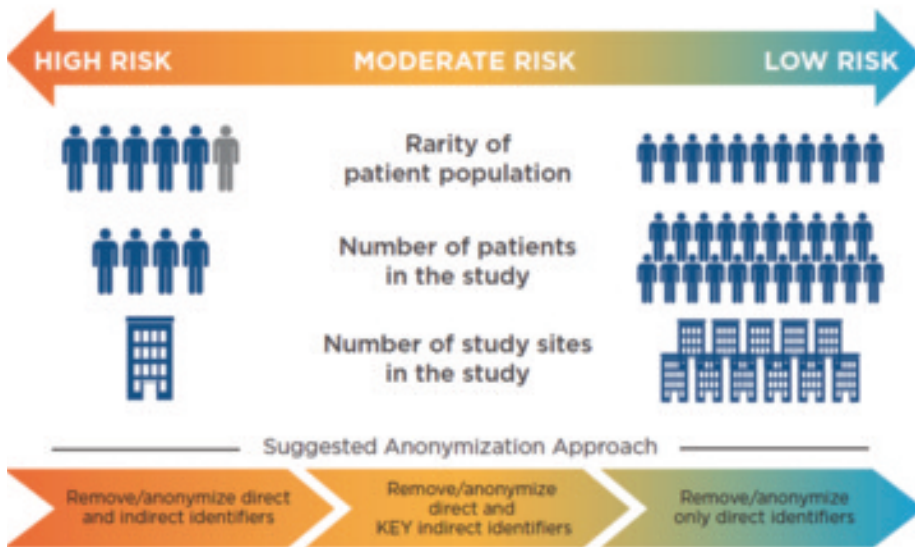
medicines, and medicines containing a new active substance to treat HIV or AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and other immune dysfunctions, and viral diseases.<sup>12</sup> Clinical documents that are made public include reports summarising clinical data at trial level (e.g., clinical trial reports, etc.) or at submission level (e.g., clinical overview, clinical summaries, etc.).

Before a document package is published on the EMA Policy 0070 website, the sponsor needs to perform several preparatory steps. The main sponsor tasks in preparing a document package are summarised in Figure 1. Within the application dossier, it is first necessary to identify the clinical reports in scope; for clinical trial reports, additionally, the sections in scope have to be determined. Further steps include the identification and protection of commercially confidential information (CCI) and personal data of the trial participants and sponsor- and non-sponsor personnel. Interaction with the EMA starts with the submission of the “redaction proposal document package”. Depending on the feedback from the EMA, the proposed package may need to be updated before it is finally submitted and made public.

## Protection of personal data and challenges involved

For the protection of personal data, an appropriate anonymisation strategy needs to be developed that balances data utility and the risk of re-identification of trial participants, taking trial-specific factors into account. To achieve this, the sponsor needs to have an overview of the trials and the type of data included in the clinical reports. As cross-referred trial reports submitted in previous procedures may also fall within the scope of EMA Policy 0070, the trial-related clinical documents in question may also include legacy trials completed many years ago. TransCelerate, a non-profit organisation of biopharmaceutical companies, has developed a qualitative approach to anonymisation based on the *rarity of the patient population*, the *number of patients in the study*, and the *number of sites in the study*,<sup>13</sup> see Figure 2. Taking these considerations into account, the sponsor has to define trial- and document-specific anonymisation rules that should ideally be agreed with the responsible data protection officer and possibly also with the competent data protection authority. The anonymisation approach that is applied to the clinical documents of a specific dossier needs to be described in an “anonymisation report”, which is also made public. Of note, although several anonymisation techniques exist (e.g., randomisation, generalisation), currently redaction is most frequently used, as shown by the dossiers published within the first year on the EMA's clinical data website.<sup>14</sup>

One challenge when protecting personal data is to ensure consistency of anonymisation across different documents, e.g., clinical reports at trial and submission level. In addition, for the development and maintenance of an appropriate anonymisation strategy, the company's transparency policy has to be aligned with applicable law and data protection regulations at a local and global level. The study of data anonymisation techniques is a vibrant field of research. Therefore, further developments in re-identification and anonymisation techniques have to be monitored and potentially implemented. This requires that companies allocate resources to both the operational dossier-specific tasks and to the maintenance of oversight of scientific and technological progress. For a summary of dossier-specific and general tasks related to the protection of personal data for EMA Policy 0070, see Table 1.



**Figure 2. Illustration of a qualitative approach to anonymisation based on the risk level of the study; developed by TransCelerate<sup>13</sup>**

### Protection of CCI and challenges involved

The identification and justification of CCI is a complex and multidisciplinary task requiring review by and input from many different subject-matter experts. As a basis, a company-wide shared understanding of which information constitutes CCI is essential. All clinical reports in scope of EMA Policy 0070 have to be screened for potential CCI. The number of pages that have to be reviewed can be substantial because, in addition to the clinical reports included in the dossier, cross-referenced clinical trial reports submitted with previous applications may also be in scope.

If information considered to be commercially confidential is identified, a sufficient and relevant justification has to be provided in “justification tables” (one per file with CCI). In addition, it has to be checked and confirmed that the CCI proposed for redaction is not yet publicly available. It is extremely challenging to submit a justification that is accepted by the EMA. Based on the first year of experience with EMA Policy 0070, the likelihood that the EMA accepts proposed CCI is very low (success rate: 0.01% of all published pages).<sup>14</sup> For a summary of dossier-specific and general tasks related to CCI protection for EMA Policy 0070, see Table 1.

### Organisational steps and further challenges

As described above, the tasks related to protected personal data (PPD) and CCI protection require close cross-functional communication and collaboration of all relevant stakeholders within a company. Firstly, the relevant internal stakeholders need to be identified; then responsibilities, interfaces, and the sequence of

interactions need to be determined and agreed cross-functionally. All functional units involved have to be trained in the requirements of EMA Policy 0070 and in their unit-specific roles. For the different tasks outlined in Table 1, the involved functional units may include members from regulatory affairs, medical writing, data transparency, legal and data protection, statistics, programming, publishing, and patents, not to mention subject-matter experts from many different areas for CCI protection. An example of the task allocation and responsibilities of the functional units is provided in Table 1.

The new EMA Policy 0070-related processes have to be incorporated into standard operating procedures or work instructions. Over time, lessons learnt and changes to the guidance have to be implemented into existing processes. Since its first publication in March 2016, the guidance on implementation of EMA Policy 0070 has already been updated three times.<sup>11</sup> Each time, the EMA introduced major changes, affecting the clinical reports in scope or substantially modifying procedural aspects, which required adaptation of established procedures and re-training of the company-internal stakeholders.

### Challenges in aligning different channels for clinical data transparency

The establishment of further channels for the public disclosure of clinical documents adds additional complexity to a company’s data transparency activities. In addition to EMA Policy 0070, [clinicaltrials.gov](http://clinicaltrials.gov) is a key channel for the disclosure of clinical trial information. Through the various channels (see examples summarised

in Table 2), different types of clinical data are made available to different audiences at different time points during drug development. The requirements for the publication of clinical documents, such as the clinical trial protocol (CTP) and the trial statistical analysis plan (TSAP), can differ greatly. For the CTP and TSAP of a trial in scope of EMA Policy 0070, the time of publication on EMA’s clinical data website is linked to the date of the commission decision or the withdrawal letter.<sup>11</sup> If these trial documents relate to a so-called “applicable clinical trial”,<sup>15</sup> they need to be published together with the structured trial results on [clinicaltrials.gov](http://clinicaltrials.gov)<sup>16</sup> at different time points, i.e., 1 year after completion of each of the following milestones: the primary endpoint, the secondary endpoint(s), and the entire trial. Moreover, the public sharing of the CTP and TSAP may be requested when the results of clinical trials are submitted as manuscripts to journals that follow the recommendations of the International Committee of Medical Journal Editors (ICMJE).<sup>17</sup>

### Transparency-ready clinical documents

To increase process efficiency and limit workload for the sponsor, transparency-ready clinical documents should be usable for all channels. However, the examples above illustrate that the time of data sharing differs between the various channels. This may lead to inconsistencies in the type and extent of information needing protection. Particularly for CCI, there is a complex relationship between the time of data release and the degree of protection needed. As some initially confidential information may be published during the drug development process, the need for CCI protection usually decreases over time. An approach to tackle this challenge is to already improve the transparency-readiness of clinical documents during writing. For example, cross-references, CCI, and PPD could be limited to the information that is necessary for standard regulatory review. Another possibility is the early identification of CCI and PPD and their mark-up in the documents for later redaction and anonymisation. It appears that the time for such efforts is well spent as there are more transparency initiatives about to be established.<sup>4,5</sup>

## Conclusion

To fulfil the EMA Policy 0070 requirements, sponsors need well-defined cross-functional

Table 1. Allocation example of sponsor tasks related to EMA Policy 0070 activities

Dossier-specific tasks	Functional unit
Interaction with EMA	Regulatory affairs
Identification of clinical reports and sections in scope for a specific dossier	Regulatory affairs, data transparency, publishing
Development of an anonymisation concept for the protection of PPD, including <ul style="list-style-type: none"> <li>• identification of data identifier categories contained in the clinical reports</li> <li>• assessment of risk level of clinical trials</li> <li>• definition of trial- and document-specific anonymisation rules</li> <li>• data utility considerations</li> </ul>	Medical writing, data transparency, publishing, legal, data protection officer, statistics and programming
Description of anonymisation approach in anonymisation report	Medical writing, data transparency, legal, data protection officer, statistics and programming
Protection of CCI, including <ul style="list-style-type: none"> <li>• review of clinical reports to identify potential CCI</li> <li>• check and confirmation of public non-availability of information</li> <li>• justification of CCI in respective table(s)</li> </ul>	Medical writing, subject-matter experts, patents
Performance or coordination of redaction/anonymisation	Publishing
Incorporation of EMA feedback on redaction proposal document package (if required) by updating <ul style="list-style-type: none"> <li>• anonymisation report</li> <li>• CCI justification table(s)</li> <li>• redaction/anonymisation of clinical reports</li> </ul>	Medical writing, data transparency, legal, data protection officer, statistics and programming, subject-matter experts, patents, publishing
<b>Tasks unrelated to a specific dossier</b>	<b>Functional unit</b>
Follow-up on regulatory and technical developments related to transparency	Data transparency, medical writing, regulatory affairs
Implementation of lessons learnt and new/updated requirements into existing processes	Medical writing, data transparency, publishing, regulatory affairs, statistics and programming
Maintenance of adequate training of all involved functional units in evolving regulatory requirements and their responsibilities for updated processes	Medical writing, data transparency, publishing
Improvement of transparency-readiness of clinical reports	Medical writing, statistics and programming

Abbreviations: CCI, commercially confidential information; PPD, protected personal data

processes with clearly defined responsibilities. In addition, the many stakeholders in a company need to be trained and kept informed of changes to the requirements. Resources need to be allocated to both the maintenance of the operational business and the oversight of regulatory changes and technological developments to ensure up-to-date company strategies and processes. As increasing numbers of national and international transparency initiatives are being established, the key challenge for sponsors is to fulfil all the non-aligned requirements and yet harmonise the data protection processes for the different publication channels. Efficient organisational structures together with increased transparency-readiness of clinical documents from the start will provide an efficient approach to meeting these demanding requirements.

### Conflicts of interest and disclaimers

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

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Table 2. A selection of existing channels for clinical data transparency

Type of clinical data	Channel	Note
Structured results	Clinicaltrials.gov <sup>a</sup>	Together with CTP and TSAP for applicable clinical trials <sup>15,16</sup>
Key findings	Publication in journals	Together with CTP and TSAP
Clinical trial synopsis	EU-CTR (clinicaltrialsregister.eu)	
	Company website	
Clinical trial report, clinical overview and summaries	EMA's clinical data website (clinicaldata.ema.europa.eu)	As part of dossiers in scope of EMA Policy 0070 <sup>3,11</sup>
Clinical trial protocol	EMA's clinical data website (clinicaldata.ema.europa.eu)	As part of clinical trial reports in scope of EMA Policy 0070 <sup>3,11</sup>
	Clinicaltrials.gov <sup>a</sup>	To contextualise structured results of applicable clinical trials <sup>15,16</sup>
	Together with a publication in a journal following the ICMJE's recommendations <sup>17</sup>	
Trial statistical analysis plan	EMA's clinical data website (clinicaldata.ema.europa.eu)	As part of clinical trial reports in scope of EMA Policy 0070 <sup>3,11</sup>
	Clinicaltrials.gov <sup>a</sup>	To contextualise structured results of applicable clinical trials <sup>15,16</sup>
	Together with a publication in a journal following the ICMJE's recommendations <sup>17</sup>	
Other clinical documents	EMA Policy 0043 <sup>9</sup>	
	Request via company website	With document sharing agreement

Abbreviations: CTP, clinical trial protocol; ICMJE, International Committee of Medical Journal Editors; TSAP, trial statistical analysis plan

<sup>a</sup> By the United States National Library of Medicine at the National Institutes of Health

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# Clinical trial results disclosure on ClinicalTrials.gov and EudraCT

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## Abstract

The range of clinical trial results information that must be made publicly accessible is ever increasing both in the United States and the European Union. This brings a number of challenges, not least maintaining consistency across the publicly available data for a given trial. Furthermore, differences exist in the specific requirements for data disclosure on the ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials databases. The planning of disclosure of clinical trial results must occur alongside preparation to author the Clinical Study Report in order to meet this important legal obligation.

With the US Final Rule for Clinical Trials Registration and Results Information Submission (42 Code of Federal Regulations Part 11)<sup>1</sup> coming into effect on January 18, 2017, and the Clinical Trial Regulation EU No. 536/2014<sup>2</sup> entering into force on June 16, 2014, the expanding scope of the public disclosure of clinical trial data has become increasingly important for sponsors of clinical trials.

## Why publicly disclose trial results?

The US Final Rule clarifies and expands the requirements for submitting clinical trial registration and results information to ClinicalTrials.gov in accordance with Section 801 of the FDA Amendments Act of 2007 (FDAAA 801).<sup>3</sup>



Failure to comply with these requirements can result in civil penalties of up to \$10 000 per day if required results are not submitted, and the withholding of grant funds for trials supported by federal agencies. However, the FDA has been criticised for never having imposed a fine on sponsors failing to publish clinical trial results.

The EU Clinical Trial Regulation will become applicable six months after the European Commission confirms that the EU clinical trials portal and database are fully functional, which is currently expected to occur early to mid-2020. The EU regulation requires member states to impose and implement penalties when the requirements are not met, stating that “The penalties provided for shall be effective, proportionate and dissuasive.”<sup>2</sup>

In addition to these regulatory penalties, the Inter-

national Committee of Medical Journal Editors now has requirements that clinical trials reported in their member journals contain a data sharing statement, either within the manuscript (as of July 2018) or within the trial’s registration (for trials that begin enrolling on or after January 1, 2019).<sup>4</sup> Data sharing statements must indicate whether individual de-identified participant data (including data dictionaries) will be shared, what data in particular will be shared, whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.), when the data will become available and for how

long, and by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism).

Recently, the Evidence Based Medicine DataLab at the University of

**The EU Clinical Trial Regulation covers all interventional clinical trials with medicinal products for human use conducted within the EU.**



Directive (2001/20/EC) and are not considered ACTs per the Final Rule. However, Phase I trials conducted solely in adults which are not part of an agreed Paediatric Investigation Plan (PIP) are not made public. Non-interventional trials and trials without medicinal products (e.g., device studies, surgery, etc.) are not within scope.

### Where are trial results posted?

Records can be prepared for disclosure on ClinicalTrials.gov directly in the web-based data entry system Protocol Registration and Results System (PRS). ClinicalTrials.gov establishes one PRS account for an organisation and this is managed by the organisation's PRS administrator. The PRS administrator can then grant individuals access to specific trials as required.

Similarly, records for disclosure in the EU can be authored directly in the EU Drug Regulating Authorities Clinical Trials databases (EudraCT) database. A primary user is assigned for a trial via the Clinical Trial Assignment Request Letter. The letter must be completed either by the sponsor, or the addressee of the decision on a PIP, or the marketing authorisation holder. The European Medicines Agency (EMA) then grants access for one primary user for the clinical trials listed in the letter who can then assign one backup user and multiple delegated results preparers and posters for each listed trial. Individual users apply for a single, personal account and are then assigned specific trials to edit by the primary user of the

trial. A template for the letter and accompanying instructions are available on the EMA website.<sup>6</sup>

In addition to authoring directly in the databases, there are specialist vendors who can offer tailored authoring software allowing users to manage the authoring, approval and release of records to PRS and EudraCT.

### What trial results are disclosed?

#### US results disclosure

The US Final Rule requires that all primary and secondary outcome measures (endpoints) are disclosed on ClinicalTrials.gov, whether or not target accrual was met, the trial was terminated, or planned analyses were expected to yield statistical significance. Careful consideration should therefore be given to which endpoints are defined as primary and secondary when drafting the protocol. Trial endpoints need to be specifically defined to avoid ambiguity over what must be disclosed at a later date. For example, stating that the pharmacokinetics (PK) of Drug X is a secondary endpoint means all derived PK parameters should be disclosed. If only certain PK parameters are of interest as secondary endpoints, these should be specified, e.g., maximum plasma concentration, area under the plasma concentration-time curve from time zero to infinity, and half-life of Drug X. If data are collected and analysed at multiple time-points, consideration should be given as to whether it is appropriate to restrict primary or secondary endpoints to particular time-point(s) of interest.

The definitions for results data that must be submitted to ClinicalTrials.gov are provided in

Oxford, UK, has developed and delivered an online tool which publicly monitors compliance with FDAAA 801 and the Final Rule, further increasing the public pressure on sponsors to adhere to the disclosure requirements.<sup>5</sup>

### Which trials must be disclosed?

In the US, the Final Rule now requires results for all applicable clinical trials (ACTs) with a primary completion date on or after January 18, 2017, to be disclosed on ClinicalTrials.gov, regardless of approval status. Previously, results were only required for approved products. Device investigations are now also within the scope of ACTs. Table 1 summarises which studies are considered within the scope of an ACT.

The EU Clinical Trial Regulation covers all interventional clinical trials with medicinal products for human use conducted within the EU. This includes Phase I trials, which were previously exempt from the EU Clinical Trials

Table 1. Applicable clinical trials per the Final Rule

In Scope	Out of Scope
Interventional clinical trials initiated on or after January 18, 2017	Phase I trials
Trials with one or more treatment arms	Device feasibility
Trials with one or more pre specified outcome measures (endpoints)	Expanded access use
Trials with at least one trial facility located in the US or a US territory	
Trials conducted under a US FDA Investigational New Drug application or Investigational Device Exemption	
Trials involving a drug, biological, or device product that is manufactured in and exported from the US (or a US territory) for investigation in another country	
Trials evaluating at least one drug, biological or device product regulated by the US FDA	
Paediatric post market surveillance of a device product	

Table 2. Content of trial results record submitted to ClinicalTrials.gov

Module	Content
Participant Flow	A tabular summary of the progress of participants through each stage of the trial, by trial arm or comparison group. Includes the numbers of participants who started, completed, and dropped out of each period of the trial based on the sequence in which interventions were assigned.
Baseline Characteristics	A tabular summary of the data collected at the beginning of the trial for all participants, by trial arm or comparison group. These data include demographics, such as age and gender, and trial-specific measures as appropriate.
Outcome Measures	A tabular summary of outcome measure values, by trial arm or comparison group. Includes tables for each pre-specified primary outcome and secondary outcome and may also include other pre-specified outcomes, post hoc outcomes, and any appropriate statistical analyses.
Adverse Event Information	A tabular summary of all serious adverse events and a tabular summary of other non-serious adverse events exceeding a specified frequency threshold (>0%, >1%, >2%, >3%, >4% or >5%). For each serious or other adverse event, the summary includes the adverse event term, affected organ system, the number of participants at risk, and number of participants affected, by trial arm or comparison group.
Limitations and Caveats	Describes significant limitations of the trial. Such limitations may include not reaching the target number of participants needed to achieve target power and statistically reliable results, or technical problems with measurements leading to unreliable or uninterpretable data.
Certain Agreements	Information indicating whether an agreement exists between the sponsor or its agent and the principal investigators (unless the sponsor is an employer of the principal investigators) that restricts in any manner the ability of the principal investigators, after the completion of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.
Results Point of Contact	Point of contact for scientific information about the clinical trial results information.

the ClinicalTrials.gov Results Data Element Definitions for Interventional and Observational Studies.<sup>7</sup> The record is divided into seven modules: Participant Flow, Baseline Characteristics, Outcome Measures, Adverse Event Information, Limitations and Caveats, Certain Agreements and Results Point of Contact. The general content of each module is provided in Table 2.

**EU results disclosure**

In contrast, the EU Clinical Trial Regulation has a less definitive description of which endpoints are required. At least one primary endpoint is

required, and the EMA recommends that data for key endpoints are disclosed rather than mandating reporting of all primary and secondary endpoints.<sup>8</sup> The EMA has previously advised that there is no link between results that must be disclosed and the primary and secondary endpoints specified in the protocol.<sup>9</sup>

Importantly, if trials are conducted both within the EU and the US, consideration must be given to ensuring the results presented on ClinicalTrials.gov and EudraCT are consistent given the different regional reporting requirements.

The definitions for results data that must be submitted to EudraCT are provided in the EudraCT Result Related Data Dictionary.<sup>10</sup> The record is divided into six modules: Trial Information, Subject Disposition, Baseline Characteristics, End Points, Adverse Events and More Information. The general content of each module submitted to EudraCT is provided in Table 3.

**Data considerations**

Data requirements should be checked carefully, ideally during production of the Statistical Analysis Plan, to ensure all required data will be tabulated and summarised. Some data, such as non-serious adverse events and the number of participants enrolled per country, are not commonly summarised for the Clinical Study Report (CSR). Detailed information on the requirements for each module can be found in the guidance documents.<sup>7,10</sup> However, a few points are worth noting and should be shared with any persons performing quality control (QC) of these records to avoid redundant QC findings:

- Fields within the database are annotated with symbols to indicate information which is mandatory, information which is conditionally required, or optional information.
- Some of the fields may only be completed by selecting from a drop-down menu thus restricting the content.
- Some fields have character limits restricting the amount of free text that can be included.

**When must trial results be disclosed?**

FDAAA 801 requires results to be submitted for ACTs no later than 12 months after the primary completion date, defined as:

*The date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.*

Results may then need to be updated following the study completion date, defined as:



Table 3. Content of trial results record submitted to EudraCT

Module	Content
Trial Information	Includes trial identification details, paediatric regulatory details, sponsor details, results analysis stage, general information about the trial, the number of participants enrolled per country and a breakdown of the trial population by age group.
Subject Disposition	Includes details of recruitment of trial participants, screening, blinding implementation, trial products, and a tabular summary of the progress of participants through each stage of the trial, by trial arm or comparison group.
Baseline Characteristics	A tabular summary of the data collected at the beginning of the trial for all participants, by trial arm or comparison group. These data include demographics, such as age and gender, and trial-specific measures as appropriate.
End Points	A tabular summary of endpoint values, by trial arm or comparison group. Includes tables for primary endpoint(s) and secondary endpoint(s) and may also include other pre-specified endpoints, post hoc outcomes, and any appropriate statistical analyses.
Adverse Events	A tabular summary of all serious adverse events and a tabular summary of other non-serious adverse events exceeding a specified frequency threshold (>0%, >1%, >2%, >3%, >4% or >5%). For each serious adverse event, the summary includes the adverse event term, affected organ system, number of participants at risk, number of participants affected, number of occurrences, number of occurrences causally related to treatment, number of fatalities, and number of fatalities causally related to treatment, by trial arm or comparison group. For each non-serious adverse event, the summary includes the adverse event term, affected organ system, number of participants at risk, number of participants affected, and number of occurrences, by trial arm or comparison group.
More Information	Includes details of substantial global protocol amendments, global interruptions to the trial, limitations and caveats and online references.

Given that no such process currently occurs for records submitted to EudraCT, addressing these NIH review comments may further contribute to inconsistencies between results disclosed in the US and EU.

The EU Clinical Trial Regulation requires a summary of results of a clinical trial to be submitted to EudraCT within 12 months of the end of the clinical trial, i.e., the last visit of the last participant, or at a later point in time as defined in the protocol. However, the regulation permits results to be submitted after this deadline if there are valid scientific reasons detailed in the protocol. In these cases, the summary of results must be submitted as soon as possible, and the protocol must specify when the results will be submitted, together with a justification for the delay. Results for paediatric trials within the scope of Article 41 or Article 46 of the Paediatric Regulation,<sup>11,12</sup> or in an agreed PIP, should be posted to EudraCT within six months of the end of the trial, unless this is not possible for objective scientific reasons.<sup>13</sup> Results for non-paediatric trials included in an agreed PIP should be posted within 12 months of the end of the trial.

**Planning results disclosure**

The length of time it takes to prepare results records will mainly be driven by the number of endpoints and any associated statistical analyses, and the number of serious and non-serious adverse events that occurred during the trial. Data can be entered manually or uploaded using Extensible Mark-up Language (XML) files. XML schemas are available online for both ClinicalTrials.gov<sup>14</sup> and EudraCT.<sup>15</sup> If both US and EU results records are required, efficiencies can be made if one record is completed prior to starting the other. Preparation of the required records should be part of the overall study timeline to ensure compliance with the regulations.

**Conclusion**

The requirements for public disclosure of trial results, including data that are not readily available as part of the CSR summary tables, should be considered in a timely manner to allow the regulations to be met. Consistency of publically available data must also be taken into account given that lay summaries and redacted CSRs will now also be released for public viewing in the EU. Although seemingly burdensome,

*The date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.*

that an ACT reached its study completion date before the drug, biologic, or device was initially approved, licensed, or cleared by the FDA for any use, or that the trial investigates a new use (i.e., not included in the labelling). A request to extend the deadline for submission of results for “good cause” can also be made.

Once results have been released via PRS, the record undergoes a QC review by the National Institutes of Health (NIH) to ensure the clarity and completeness of the information submitted. It is important to

Of note, if the primary completion date and study completion date occur in close proximity, it may be possible to submit one record within the 12-month deadline.

Results disclosure on ClinicalTrials.gov may be delayed by submitting a certification

**Preparation of the required records should be part of the overall study timeline to ensure compliance with the regulations.**

note that the record will not be released publically until it passes this QC step and to do so may take several iterations.



complying with the disclosure regulations can only have a positive impact on the wider public perception of the pharmaceutical industry.

## Disclaimers

The views expressed in this article are those of the author and do not necessarily reflect those of ICON Clinical Research United Kingdom Ltd or EMWA.

## Conflicts of interest

The author is employed by ICON Clinical Research United Kingdom Ltd.

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# Writing lay summaries: What medical writers need to know

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## Abstract

Lay summaries are critical for building public trust in clinical research and therefore for recruiting patients. They are also an important part of efforts to improve data transparency. Due to new global regulations, lay summaries will soon probably become mandatory for all clinical studies. Medical writers should therefore be aware of the regulations and essential content of lay summaries. Using a case study of a published lay summary, this article discusses best practices, including the appropriate target audience, language, and data and visual presentation.

## What are lay summaries?

Understanding clinical studies is important not only for healthcare professionals but also patients (see Box 1).<sup>1,2</sup> A major concern, however, is whether the participants can understand the technical terms employed. Lay summaries were created to address this need. They briefly explain the results of a clinical study in non-technical language. This allows patients to be informed of what happened in the study, helps to recruit participants for future trials, and reinforces patient trust in clinical research.<sup>2</sup> Lay summaries are also important for transparency and thereby help improve the overall quality of clinical

### Box 1. Public attitude toward clinical studies

A global survey in 2017 of more than 12,000 respondents (including patients and the general public) by the the Center for Information and Study on Clinical Research Participation found that 85% of the public valued clinical studies for developing new medicines and considered clinical studies to be safe (90%).<sup>3</sup> The survey also found that 84% considered it important to be aware of the clinical studies being conducted in their communities, and 91% believed that it is important to receive a summary of the study after they participated in a clinical study.

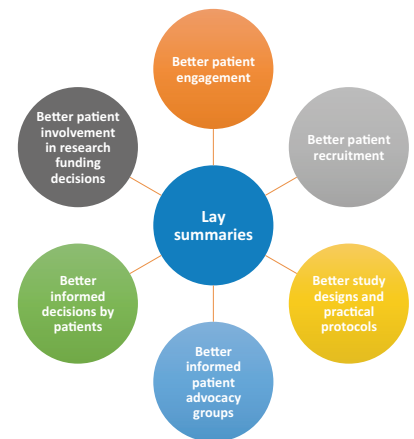


Figure 1. Benefits of preparing lay summaries.

research. The benefits of lay summaries are illustrated in Figure 1.

## Regulatory requirements of lay summaries

The Declaration of Helsinki<sup>4</sup> considers the dissemination of clinical study results crucial. It states that “all medical research subjects should be given the option of being informed about the general outcome and results of the study”.

Further, EU Clinical Trials Regulation 536/2014 states that sponsors should provide a summary of clinical trial results in a format that can be understood by a lay audience (i.e., lay summaries) within a year after a trial is

completed.<sup>5,6</sup> Although the regulation was adopted in 2014, it is expected to not be fully applied until 2019 when the EU database that includes lay summaries will become fully functional.<sup>7</sup> In the US, lay summaries are not included in the Final Rule on registering clinical trials and submitting results, although the US FDA encourages providing lay summaries to the participants of clinical studies.<sup>8,9</sup>

Since the regulations on lay summaries are about to change, various organisations and pharmaceutical companies have collaborated to meet the standards. Since 2011, the Center for Information & Study on Clinical Research Participation, in association with several global pharmaceutical companies, has been helping to translate the technical results of clinical studies into lay summaries.<sup>10</sup> Also, TrialScope, in partnership with AstraZeneca, recently launched a Trial Results Summaries Portal where sponsors can post lay summaries for study participants and the general public.<sup>11</sup>

Due to changing regulations, and growing interest of patients (and the general public), lay summaries are becoming mandatory worldwide. Medical writers therefore should be aware of their content and style.

## Key elements of a lay summary

According to Annex V of the EU Clinical Trials Regulation, lay summaries should include 10 essential elements describing details of the clinical study design and conduct, the medicinal product tested, and overall results.<sup>5</sup> These are summarised in Box 2.

However, Annex V does not provide

explanations or instructions about the format, length, or language. To fill these gaps, a task force has assembled more detailed guidance entitled “Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use”.<sup>6</sup> This guidance not only gives an explanation of the 10 essential elements but also provides some instructions on writing style, language, numbers, visuals, and other important aspects of a lay summary.

## Content of a lay summary: A case study

To illustrate the type of information to be included in each section, we studied a published lay summary on pregabalin,<sup>12</sup> a drug for treating diabetic neuropathy.<sup>13</sup>

### Title page

The lay summary starts with a title page (Figure 2) that provides basic information about the study like the sponsor, drug studied, trial number, and study dates. Identifying information for the study is at the top of the page, and following a “thank you” message, the study is introduced:

*“Thank you for participating in the clinical trial for the drug pregabalin, which took place between March 2010 and January 2012.”*

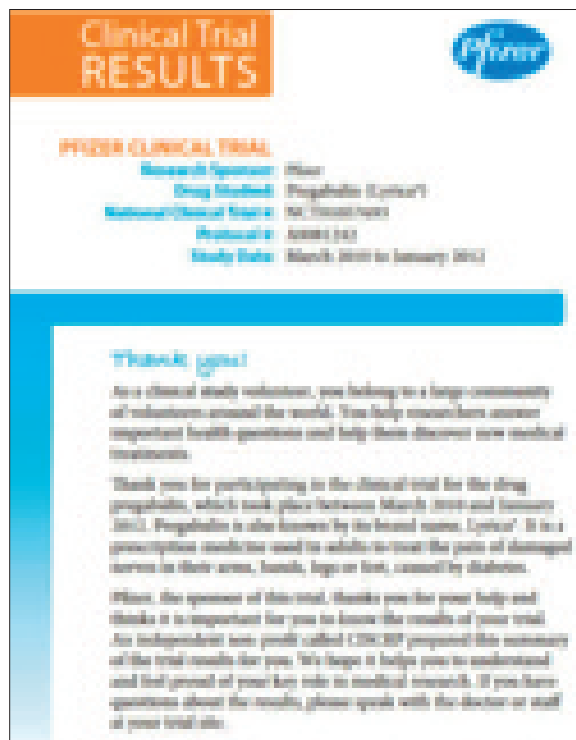


Figure 2. A typical lay summary: first page.

Source: Center for Information & Study on Clinical Research Participation.<sup>12</sup>

The section then describes the drug and its use in a non-technical language:

*“Pregabalin is also known by its brand name, Lyricon®. It is a prescription medicine used in adults to treat the pain of damaged nerves in their arms, hands, legs or feet, caused by diabetes.”*

This is followed by a simple thank you note from the sponsor that also highlights the importance of patients in clinical research, building trust and confidence in the study.

*“Pfizer, the sponsor of this trial, thanks you for your help and thinks it is important for you to know the results of your trial... We hope it helps you to understand and feel proud of your key role in medical research.”*

### Second page

The second page of this lay summary (Figure 3) describes the study rationale and design and provides an explanation of what has occurred since the study was completed.

### What’s happened since my trial ended?

This section gives an overview of study duration, number of participants, and what was done when the study ended:

*“The entire study took almost 2 years to finish, and included 665 volunteers at 129 locations in*

### Box 2. The 10 essential aspects of a lay summary<sup>6</sup>

1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers).
2. Name and contact details of the sponsor.
3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it).
4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria).
5. Investigational medicinal products used.
6. Description of adverse reactions and their frequency.
7. Overall results of the clinical trial.
8. Comments on the outcome of the clinical trial.
9. Indication if follow up clinical trials are foreseen.
10. Indication where additional information could be found.

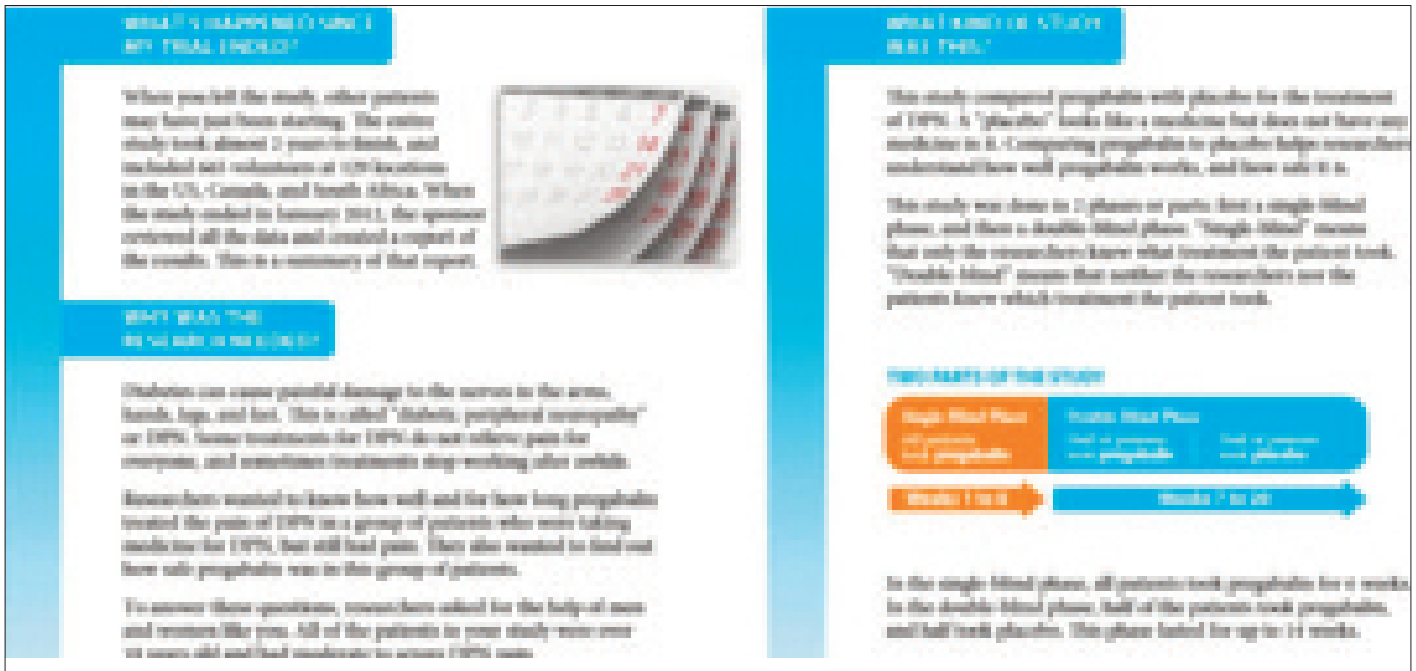


Figure 3. A typical lay summary: second page. Source: Center for Information & Study on Clinical Research Participation. 12

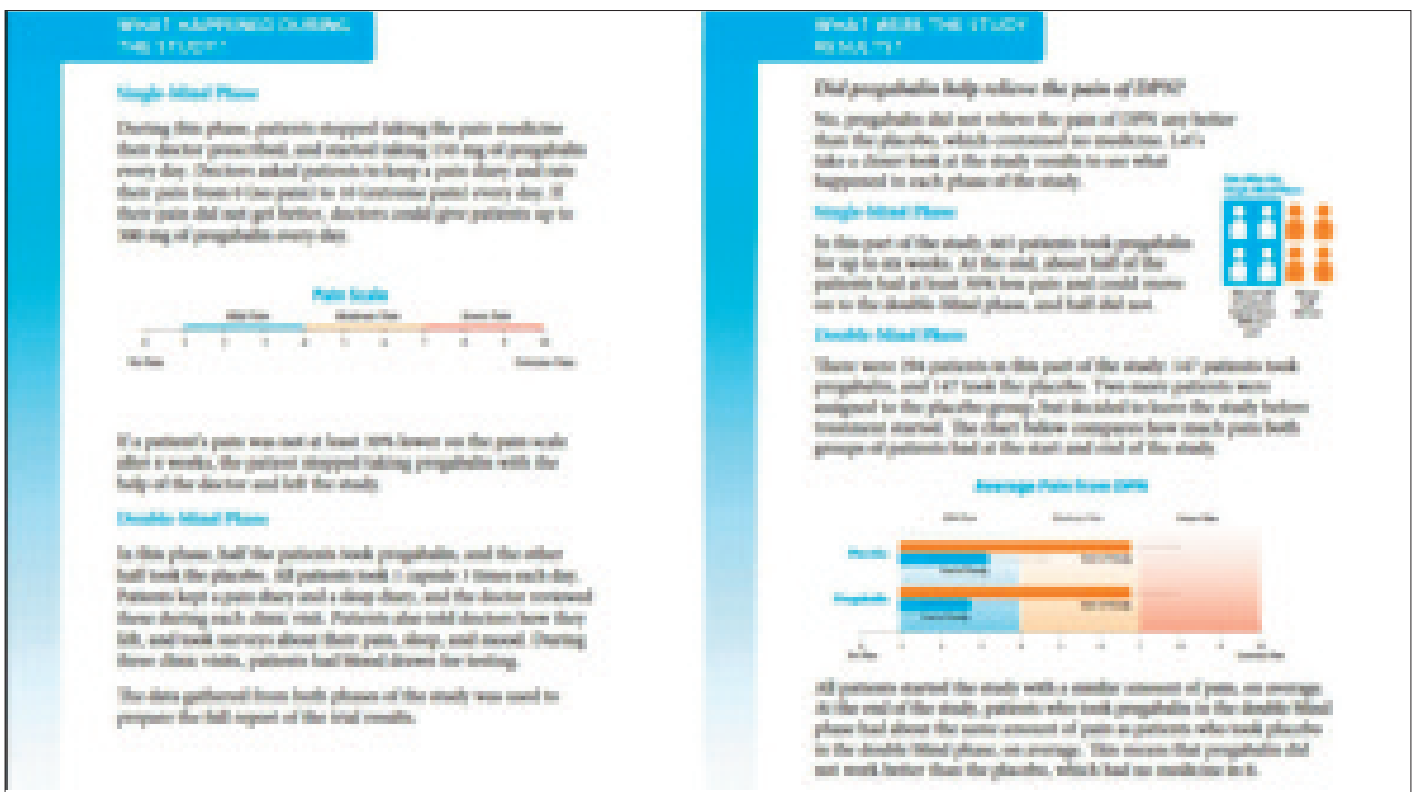


Figure 4. A typical lay summary: third page. Source: Center for Information & Study on Clinical Research Participation. 12

the US, Canada, and South Africa. When the study ended in January 2012, the sponsor reviewed all the data and created a report of the results."

**Why was the research needed?**

This section describes the rationale for the study

in language that can be understood by a layperson:

"Diabetes can cause painful damage to the nerves in the arms, hands, legs, and feet. This is called diabetic peripheral neuropathy (DPN). Some treatments for DPN do not relieve pain for

everyone, and sometimes treatments stop working after a while."

The section also explains what the disease is and why the sponsors are interested in performing this study:

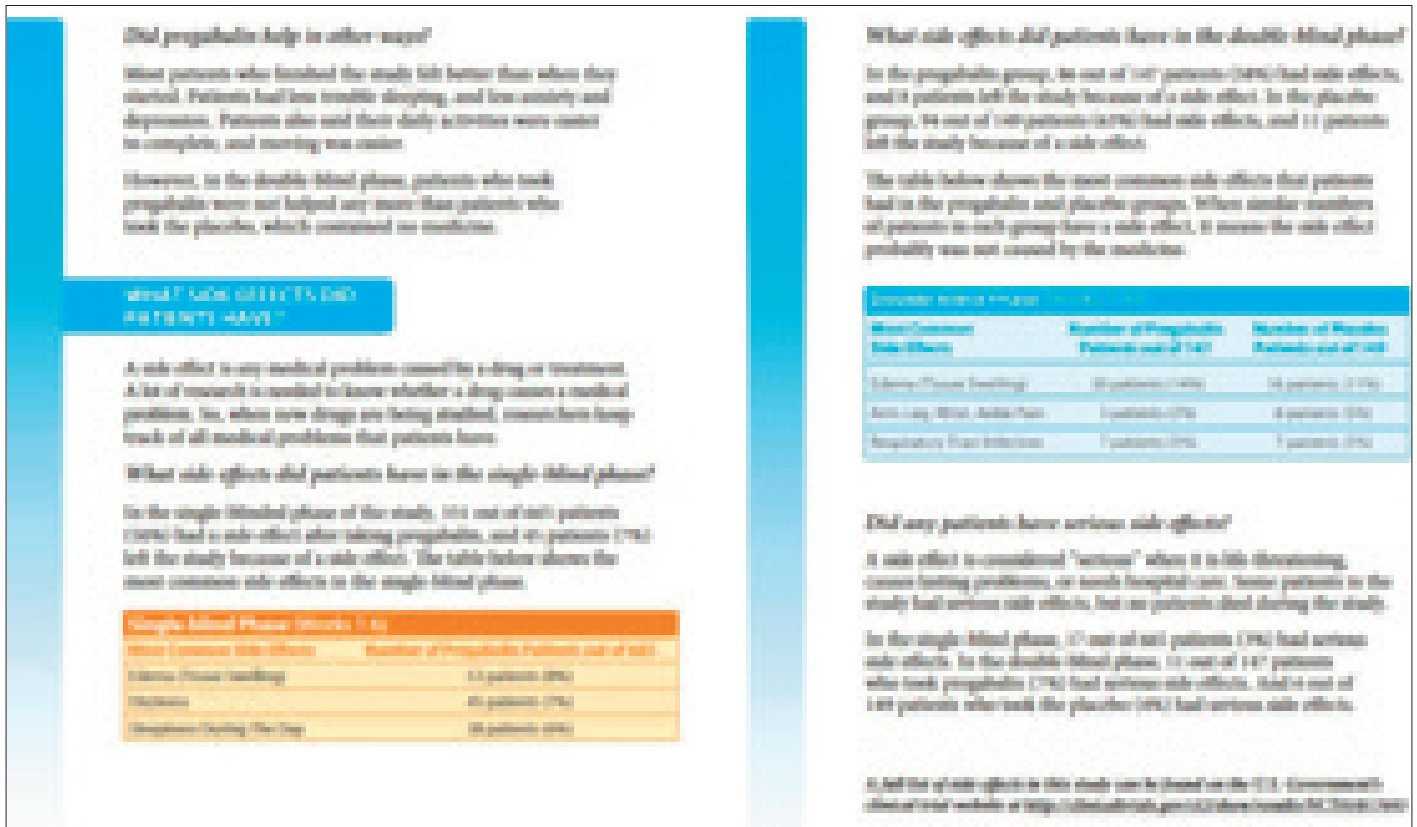


Figure 5. A typical lay summary: fourth page. Source: Center for Information & Study on Clinical Research Participation. 12

“Researchers wanted to know how well and for how long pregabalin treated the pain of DPN in a group of patients who were taking medicine for DPN, but still had pain. They also wanted to find out how safe pregabalin was in this group of patients.”

**What kind of study was this?**

Because patients and the general public will not understand the study design, this section aims to explain technical terms like “blinded”, “placebo”, “randomised”, and “crossover” using non-technical language. Diagrams or figures are used to explain terms that are otherwise difficult to understand.

“This study compared pregabalin with placebo for the treatment of DPN. A “placebo” looks like a medicine but does not have any medicine in it. Comparing pregabalin to placebo helps researchers understand how well pregabalin works, and how safe it is. This study was done in 2 phases or parts: first a single-blind phase, and then a double-blind phase.”

An explanation of “single-blind” and “double-blind” and a figure to help explain the two parts of the study are also included.

**Third and fourth pages**

The third and fourth pages of this lay summary (Figures 4 and 5) describe the study conduct, outcome assessments, and results using non-technical language.

**What happened during this study?**

This section briefly explains the treatment procedures, medications given, how they were administered, and what the patients were asked to do.

“In this phase, half the patients took pregabalin, and the other half took the placebo. All patients took 1 capsule 3 times each day... Doctors asked patients to keep a pain diary and rate their pain from 0 (no pain) to 10 (extreme pain) every day... Doctors reviewed these diaries during each clinic visit.”

As with the study design, an illustration is used to help explain.

**What were the study results?**

This section gives details on the study results, for example, if the medication was effective, how many patients benefited from the treatment, and additional benefits of the treatment. Numerical data can be presented as tables or, as in this example, figures to help aid understanding.

The section starts with a bottom-line summary of the study findings:

“No, pregabalin did not relieve the pain of DPN any better than the placebo, which contained no medicine.”

This section then details what happened in the different parts of the study, including how many patients were included in each study group and what happened to patients. A conclusion for each part of the study is also provided. Finally, the section concludes (on the fourth page) with information about any additional benefits of the treatment:

“Most patients who finished the study felt better than when they started. Patients had less trouble sleeping, and less anxiety and depression.”

**What side effects did patients have?**

Apart from understanding whether the treatment was effective, patients and the public need to be confident that it was safe. Because their understanding of medical terminology is very limited, this section needs special care. As in other sections, numerical data can be presented in tables, as in this example, or as figures. The section begins with a general explanation of side effects:

“A side effect is any medical problem caused by a

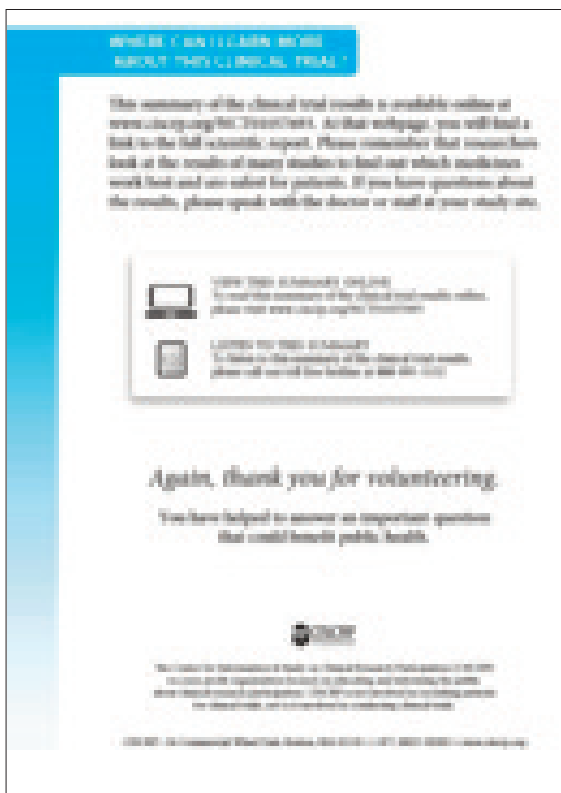


Figure 6. A typical lay summary: last page.

Source: Center for Information & Study on Clinical Research Participation.<sup>12</sup>

drug or treatment. A lot of research is needed to know whether a drug causes a medical problem. So, when new drugs are being studied, researchers keep track of all medical problems that patients have.”

This is followed by the safety findings from the different parts of the study:

“In the single-blinded phase of the study, 331 out of 665 patients (50%) had a side effect after taking pregabalin, and 45 patients (7%) left the study because of a side effect. The most common side effects were: edema (tissue swelling), dizziness and sleepiness during the day.”

Table 1: Examples of plain-language replacements for technical terms to use in lay summaries

Avoid using	Consider using
Hyperglycaemia	High blood sugar
Hypertension	High blood pressure
Leucocytes	Blood cells that fight infection
Angina	Chest pain
Metastasis	Spread of cancer
Adverse drug reaction	Side effect
Inflammation	Swelling

After that, serious side effects, including a general explanation, are described:

“A side effect is considered “serious” when it is life-threatening, causes lasting problems, or needs hospital care. Some patients in the study had serious side effects, but no patients died during the study.”

**Last page**

**Where can I learn more about this clinical trial?**

This section informs patients and the general public about how to obtain further information about the study (Figure 6):

“This summary of the clinical trial results is available online at [www.cisr.org/NCT01057693](http://www.cisr.org/NCT01057693). At that webpage, you will find a link to the full scientific report... If you have questions about the results, please speak with the doctor or staff at your study site.”

The web address is also provided in a box at the bottom along with a phone number to listen to the lay summary.

**Best practices for writing a lay summary**

**Audience**

Keep in mind that the summary is meant for general public or study participants. This audience will not be familiar with medical terminology, so the lay summary needs to be written using non-technical terms. To avoid boring the reader, the lay summary must not be too long or too simple. This can be best achieved by having patients, members of the general public, or patient advocacy groups participate in preparation of lay summaries through user testing.<sup>14,15</sup>

**Language**

The text in a lay summary should be written for a grade 6–7 reading level. The study rationale should be explained in plain language and should provide background information about the disease and drug studied. Sentences should not be too long, and technical terms should be replaced by plain-language words or phrases (see Table 1). Of course, long sentences cannot always

be avoided, for example, when explaining certain technical terms. In such cases, an illustration may help.

Active voice should be used to engage the reader and is most effective at communicating the information. Further, the text must not be too promotional to avoid misleading the reader. For example, saying that “drug X is effective in treatment” can be misleading because the summary is for a particular study, whereas the drug label is based on several studies. Another example is that although a phase 2 study might have provided promising results, they need to be confirmed in a phase 3 study, so great care should be taken when making statements about efficacy or safety. Finally, to ensure that the included patients and local public are informed, lay summaries should be translated into the language where the study was conducted.

**Visual presentation**

Lay summaries can include visuals to aid understanding and make the summaries more appealing. Although visuals such as infographics do not improve comprehension, they are more enjoyable and user-friendly.<sup>16</sup> To avoid misinterpretation, visuals should be simple and accompanied by text. The text itself can also be improved by using visual elements like headings, subheadings, bullet points, and sidebars.

**Data presentation**

Numerical data are always difficult to comprehend when presented as text. To improve comprehension and presentation, they can instead be provided in tables and figures.

**Disclaimers**

The most important concern for lay summaries is that the general public may misinterpret the results and draw conclusions that go beyond the limitations of the study. For example, it is inappropriate to conclude that a drug is beneficial based on the results of a single study. Thus, lay summaries should always be accompanied by disclaimers stating that results of a particular trial do not display the complete medical picture and that patients should always consult their doctor before changing their on-going therapies.<sup>17</sup>

**Conclusion**

Making the results of clinical research available

to patients and the general public is critical for improving awareness and therefore health outcomes. Lay summaries accomplish this by providing the results in a plain language. The EU Clinical Trials Regulation, which will come into force in 2019, mandates the posting of lay summaries in the EU database. Thus, medical writers need to be aware now about the importance of and best practices for preparing lay summaries.

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## Disclaimers

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

## Conflicts of interest

The authors disclose no conflict of interest.

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# Lay titles for clinical trials: A balancing act

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## Abstract

With increasing transparency demands and the new legal requirements for providing clinical trial information to lay readers, clinical trials need to be given titles that patients can understand and recognise. Trial titles inform the readers what the trial is about, what substances are studied, and who the target population is. Devising a lay title is challenging as it needs to be understandable to lay readers, fully identify the trial, meet registry requirements, and also be translatable into different languages. Lay titles also need to fit different types of documents, e.g. trial protocols, trial advertisements, informed consent forms, and lay summaries. As the lay title is one of the first pieces of information that is displayed, good lay titles help patients searching clinical trial registries for trial participation. For sponsors, informative and understandable lay titles increase the chances of attracting the target patient populations for clinical trials.

Every clinical trial protocol needs a title to define and identify the trial. This title serves as a point of reference within the sponsor organisation, with ethics committees, institutional review boards, and regulatory authorities. The scientific title is developed by the trial sponsor and is primarily written for medical experts who read the protocol and may become investigators in the trial. The scientific title therefore needs to provide a



considerable amount of detail. It informs investigators about the objective of the trial, its main design features, the key characteristics of the trial participants, the medical procedures to be performed, and other information considered important. This results in trial titles that are complex and highly condensed, aiming to convey a maximum of information using technical language, sometimes with abbreviations and acronyms only familiar to medical specialists. The title usually includes specific trial features (e.g. randomisation, blinding, placebo, or active controls) to help identification within electronic databases. The CONSORT 2010 statement<sup>1</sup> recommends including the word “randomised” in the trial title to ensure that the trial is identified as a randomised trial. Scientific trial titles, written for the scientific community, are usually too complex to provide insightful information to patients and the general public.

Increasing transparency demands and legal requirements for the provision of clinical trial information to the public, as well as the need to demonstrate scientific integrity, have led to the mandatory registration of clinical trials in public registries. In general, all clinical trials involving human subjects need to be registered before trial start.<sup>2,4</sup> Many major medical journals will not publish results of trials that have not been registered.<sup>3</sup> In addition to the scientific title, many registries require trials to have a version of the title that is understandable for the lay public.<sup>4</sup> Most importantly, ClinicalTrials.gov requires that every trial posted must have a brief title “written in

language intended for the lay public”.<sup>5,6</sup> However, the terminology used by ClinicalTrials.gov is confusing as the word *brief* only addresses length restrictions and does not convey the notion of lay-friendliness that is required according to ClinicalTrials.gov instructions.<sup>6</sup> We will therefore use the term “lay title”. Trial registries are searchable by patients and the title is usually the first and most prominent piece of information about a trial they will encounter. Attractive and understandable titles help lay readers decide whether they should continue reading or focus on other registry entries.

Trial titles that are understandable for lay readers are needed for several trial-related documents (see Figure 1). These include informed consent forms, trial advertisements, and lay summaries of clinical trial results.<sup>7</sup> For the public, the lay title is the main identifier of a trial. Therefore it is important that each trial has only a single lay title that is used across all documents.

## Lay titles and patient engagement

Depending on the disease, clinical trials are an important option for patients to receive innovative treatment. Patients who are searching for clinical trials need to be able to readily determine whether any given trial is of interest to them. For sponsors, it is important to inform potential participants about available trials as this supports recruitment and hence accelerates clinical development. The lay title is often the first element of contact between the patient and the

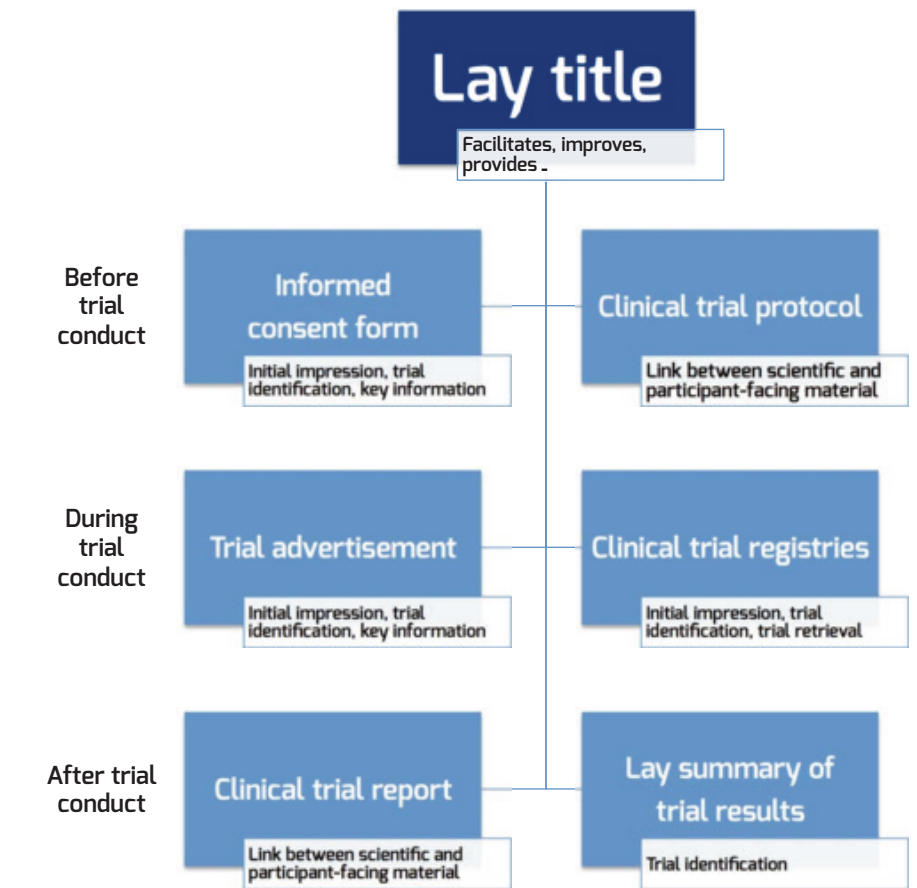
trial. Sponsors of clinical trials have several ways to inform patients about trials they could participate in. In addition to large registries such as ClinicalTrials.gov, information about clinical trials is available via local and national trial finders and databases of hospitals, charities, and patient advocacy groups. Most of these databases include a lay title in addition to the scientific title, while some only include a lay title without providing the scientific title at all. Many databases import their data, including the lay title, directly from ClinicalTrials.gov. The words used in the lay title will therefore determine how likely a patient is to find the trial. As a consequence, the lay title might be the single most important sentence of a trial's public posting. By ensuring that the lay title is informative and understandable, sponsors can attract the appropriate target patient population. This can be done not only via registry entries but also in trial-specific advertisements either online, in print media, or via other channels. To help potential trial participants understand the purpose of a trial, lay titles should also be used on informed consent forms or trial information leaflets.

In addition to the many uses of lay titles at the outset of clinical trials, lay trial titles are also relevant after completion of a trial. A good lay title will help sponsors to ensure that patients and their doctors can find the results of clinical trials they participated in or of other trials that are also relevant for them. Therefore, the lay title should also be mentioned on the lay summary detailing the clinical trial results.

### What are the challenges in writing lay titles?

As mentioned above, trials should have a single lay title in all documents for trial participants and the general public. The most stringent requirements for lay titles seem to be those of ClinicalTrials.gov (see Table 1). The requirements of ClinicalTrials.gov concern both technical and content aspects for lay titles. Apart from the formal requirements, our experience is that ClinicalTrials.gov reviewers may sometimes have additional requests. Examples of such requests are that titles comprise a single sentence, that they should not have a full stop at the end, and that trial acronyms are included only at the end of the title.

Lay titles on ClinicalTrials.gov need to be unique.<sup>8</sup> This is important when searching for trials in order to differentiate between similar trials. However, it is more difficult to provide



**Figure 1. The need for a harmonised lay title across a range of clinical trial documents and the information it provides for each document.**

“Trial identification” means that the lay title serves as the key identifier for the participant-facing material for a particular trial. “Trial retrieval” refers to the importance of the lay title for the identification of trials using a given search term.

unique lay titles than unique scientific titles because lay titles mention fewer distinguishing features of a trial. Especially in the early stages of clinical development, individual trials may not

differ much from one another and subtle differences between trials may be difficult to convey with their lay titles. Examples include the single rising dose and multiple rising dose Phase

**Table 1. Lay title requirements by ClinicalTrials.gov**

Requirements for the brief title in ClinicalTrials.gov <sup>5,6,8</sup>		Our experience based on frequent interactions with ClinicalTrials.gov reviewers*	
Technical requirements	Content	Content not to be included	Possible other format items
Maximum of 300 characters including spaces	Intervention	Phase	Need to explain abbreviations
Has to be biunique	Condition	Randomisation	Should only be 1 sentence
	Target population	Blinding	Should not have a full stop at the end
	Scientific aim		Trial acronym should be at the end

\*These are expectations that have occasionally been provided as feedback from ClinicalTrials.gov reviewers. As this did not happen for all lay titles, these items seem to depend on the individual ClinicalTrials.gov reviewer.

Table 2. Examples for lay titles for different trials

**Type of title****Example trial 1**

Scientific title	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising intravenous doses of Testdrug in healthy male subjects (single-blind, partially randomised, placebo-controlled design)
Sentence	This study in healthy men tests how different doses of Testdrug are taken up in the body and how well Testdrug is tolerated.
Title format	A study to find a suitable dose of Testdrug in healthy men and to test how different doses of Testdrug are taken up in the body

**Example trial 2**

Scientific title	A randomised, double-masked, double dummy, placebo and active controlled study to evaluate the efficacy, safety and tolerability of orally administered Testdrug for 52 weeks in patients with mild visual impairment due to center-involved diabetic macular edema (DME). ACRONYM1
Sentence	This study tests how well Testdrug is tolerated and how effective it is. This is studied in patients with mild eye problems because of diabetic macular edema. ACRONYM1
Title format	Effects of Testdrug in patients with mild eye problems because of diabetic macular edema – ACRONYM1

I trials, where the only distinguishing feature is how often the substance is taken.

Because of length and content restrictions, as well as the need to translate medical concepts into lay language, it is inevitable that lay titles deviate from the scientific title. The translation of complex medical or technical concepts into lay terms often increases word count and is one reason why a lay title can only provide a limited amount of detail about the trial. It may be difficult to include specific details on trial design, procedures, or patient population while adhering to requirements for length and lay language. As a result, some ethics committees might find that a lay title provided on the patient information or informed consent form does not include all important information, or that it is not consistent with the scientific title. The challenge for the sponsor is to find the appropriate balance between adhering to registry requirements, making the title understandable for the lay reader, and staying as close as possible to the scientific title.

## How can sponsors write a good lay title?

A well-written lay title is not only easy to read but also informs the reader what the trial is about, what interventions are studied, and who the target population is. A poorly written lay title could

mean that patients miss the opportunity to participate in clinical trials that could be of benefit to them.

There are a few general considerations when it comes to writing a good title. The title should be informative to the reader and as specific as possible.<sup>9,10</sup> It should also be concise – not only to meet formal requirements, but also because short titles are more likely to make an impression with readers and to be remembered.<sup>9,10</sup> Titles also need to be accurate and care must be taken not to be misleading about potential benefits of the intervention being investigated.<sup>11</sup> Including details on the research design in the title may be informative but this usually comes at the expense of conciseness.<sup>9</sup>

To ensure consistency and quality, lay titles should ideally be written by a single function. We believe that medical writers are best suited to writing lay titles. Medical writers as language experts can balance the competing aims of providing a title that is informative, compliant with regulations and guidelines, and understandable for patients. A key role of medical writers is to develop consistent standards and messages across a range of different documents. This also applies to lay titles. A good tool to ensure consistency across lay titles is a continuously updated repository of all lay titles that have already been

provided by the sponsor. Collecting information about the trial, such as the scientific title, the clinical phase, or the indication can help immensely in the development of standards and in harmonisation across trial designs and therapeutic areas.

### Content of a lay title

The lay title gives patients an immediate impression of what the trial is about. At a minimum, the lay title should include the name of the substance or intervention, the target population, and ideally the aim of the trial. For the name of the substance, the choice is between the international nonproprietary name (INN), the lab code, and the tradename. The advantage of the tradename is that it is most likely to be recognised by patients. However, tradenames can differ by country and region and might also change over time. Our recommendation therefore is to use the INN, but if no INN is available, the lab code could also be used.

The description of the target population usually means including the name of a specific disease or subtype of a disease. The names of common diseases (e.g. diabetes, asthma) are often well known to the general public and are therefore likely to be understood if included in lay titles. Rarer diseases and those with complicated medical names (e.g. palmoplantar pustulosis, non-valvular atrial fibrillation) will not be understood by members of the wider public but are likely to be known to patients with that particular diagnosis. To make the lay title meaningful for the wider population but specific enough for the target population, it can be helpful that the title includes both the wider concept of the disease as well as the medical name, for example “...in patients with the skin disease palmoplantar pustulosis”. If length permits, we recommend including additional details about the patient population. Including information on sex, required age range, or required background medication can all help the title address the relevant patient population.

Describing the aim of the trial within the constraints of a lay title can be challenging. We recommend focusing the lay title on the primary objective of the trial, even if that means losing some information that is provided in the scientific title. It is also useful to define standard phrases for specific scientific terms. For example, “pharmacokinetics” in the scientific title can be written as “how [substance X] is taken up by the body” for

the lay title. Such an approach also helps to achieve harmonisation across different trials. It might also be useful to consider how frequently certain words are used in everyday language.

To keep the lay titles for similar trials unique, adding the trial acronym is recommended, provided one is available.<sup>8</sup> The disadvantage is that trial acronyms might be cryptic, difficult to read, and thus likely to cause confusion for a lay reader.<sup>11</sup>

The use of abbreviations in titles has both advantages and disadvantages. Abbreviations in lay titles could be perceived as helpful by laypersons because they reduce the number of complicated, technical words and might in some cases be more common than the long form (e.g. HIV). On the other hand, ClinicalTrials.gov requires abbreviations to be explained at first occurrence,<sup>12</sup> which is technically the lay title.

#### Format and structure of a lay title

There are several structure and format considerations that authors need to think about when writing lay titles. One is whether to use a classic title format or a sentence (see Table 2). A sentence format might be easier to read for laypersons because complex information can be divided over two short sentences. The sentence format allows adding more specific details about the trial, which may help patients identify relevant trials and also helps keep titles unique. However, titles over two sentences or more are not always accepted by ClinicalTrials.gov reviewers (see Table 1). Furthermore, readers are often not familiar with a sentence format for titles and may even not recognise it as a title. The reason for this is that we are all trained to recognise a line of text as a title because of its location and its structure. In everyday life, titles do not follow the conventional sentence structure of subject, verb, and object. Instead, they are fragments of text that anticipate the subsequent content.

As the lay title will be used on documents at any time during the conduct of the clinical trial, it should be in the present tense. Titles should be written in the active rather than the passive voice because active voice is clearer and easier to understand.<sup>13</sup>

Lay titles often need to be translated to other languages. Some words and phrases are hard to translate into certain languages. In some cases a word for word translation might lead to a misleading description of the trial. As the translator might not be familiar with the medical

content, it is important to use language that is as clear as possible.

## Conclusions

Clinical trials need to have titles that can be easily understood by laypersons. A good lay title can help patients find an appropriate trial for their condition, and sponsors in the recruitment of the relevant target population for clinical trials. The lay title is the link between different trial-related documents from trial registration to the provision of trial results. Writing a lay title is a balancing act between registry requirements, readability for lay audiences, level of detail required and permitted, and reflecting the trial design and objective.

## Conflicts of interest

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

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# Why clinical study reports really matter

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## Abstract

Clinical study reports (CSRs) have so far served as documents for drug approval, but not as a data source for further use in research and post-regulatory decision-making. Sound post-regulatory decisions also require data other than those available in publications due to reporting bias found in literature. At present, CSRs are the only documents that are comprehensive enough to solve this problem. Developments being carried out by the EMA and journal editors towards data transparency may place CSRs as future core documents.

For many medical writers, preparing clinical study reports (CSRs) is a major part of regulatory medical writing. Most CSRs are conducted or commissioned by pharmaceutical companies and targeted to regulatory agencies (e.g., EMA, FDA), which use CSRs as a basis for their decisions. Until recently, the content of CSRs was classified as commercially confidential information (CCI). In consequence, access to CSRs was mainly limited to regulatory bodies, which in turn merely published parts of the data obtained from CSRs in their reports, such as the EMA's European Public Assessment Reports.<sup>1</sup> Thus, one may be tempted to assume that CSRs are written for the archives of pharmaceutical companies and drug authorities and are only sometimes resurrected as data source for selected publications in scientific journals or conference proceedings. However, the need for clinical study data does not end with the approval of a new drug.



## Post-approval decisions and the need for complete data

Post-approval decision-making involves far-reaching questions. One is whether a new drug does indeed have an added benefit over the existing standard of care. The task of answering this is usually performed by a country's health technology assessment (HTA) agency, and the answer is required first, to support decisions on reimbursement and pricing, and second, to ensure the development of high-quality clinical guidelines and patient information. If complete

information on treatment options is available, then individual patients, together with their physicians, can decide whether they wish to use a certain drug in their specific situation. This ensures patient autonomy, which is in itself a criterion resulting in better treatment and ultimately in high-quality health care.

Regulatory agencies and post-approval decision-makers have different aims, tasks, and concerns. For example, HTA agencies and health policy decision-makers usually place greater emphasis on a new drug's relative effectiveness

(i.e., on added benefit versus harm as well as on cost-effectiveness) than do regulatory bodies. In addition, there are differences in local settings such as the availability and reimbursement policies between countries. Therefore, local HTA agencies and health policy decision-makers often require a different set of data. The same applies to the authors of clinical guidelines, which are largely developed within the context of the conditions of a specific health care system. In spite of these differences, the evidence divide between regulatory bodies and policy makers must be overcome.

As mediators in attaining high-quality health care, HTA agencies, as well as authors of clinical guidelines and patient information, should not have to rely on selective and limited information available in journal publications, but should have access to complete information, i.e., methods and results of all relevant studies.

## Criteria for valid decision-making in managing health care

Data from all relevant studies are required to adequately inform all of these stakeholders. They must be available in a high-quality publication format. A valid interpretation of study results is only possible if the following requirements are met:

1. All study methods as specified in the protocol must be reported, including patient selection, mode of randomisation and blinding, study treatments and comparators, definition of outcomes, data collection, and statistical analysis.
2. Changes to the study protocol must be documented clearly and with sufficient justification.
3. Study results must be presented in an adequately aggregated form as specified in the protocol (and, for specific research questions, as individual patient data).
4. Both study methods and results must be presented in a level of detail that allows critical appraisal of the study.

Unfortunately, these requirements are currently far from being met, as reporting bias is still a common problem.

## Reporting bias

Publication bias and outcome reporting bias represent two types of reporting bias and refer to

bias caused by missing data at two levels: the study level, i.e., “non-publication due to lack of submission or rejection of study reports”, and the outcome level, i.e., “the selective non-reporting of outcomes within published studies”.<sup>2</sup> A body of evidence dating back several decades ago<sup>3</sup> demonstrated that reporting bias is a universal problem in medical research. It may not be surprising that study results showing positive results of new drugs are published more rapidly and more often than those with negative or neutral results.<sup>2,4,5</sup> Therefore, published literature may overestimate beneficial effects, while harms are underestimated.

However, until the past decade little was known about the measurable impact of reporting bias on the health care system. This changed in 2006, when The Cochrane Collaboration published a systematic review on the efficacy of the neuraminidase inhibitors (NIs) oseltamivir and zanamivir in the prevention and treatment of influenza. In their original publication, they concluded that NIs were effective in reducing complications of influenza in otherwise healthy adults.<sup>6</sup> In 2009, however, they became aware that their review was based on a single manufacturer-funded study using unpublished data. So in order to update their report, they asked the manufacturer of oseltamivir, Roche, for all data (see Doshi 2009<sup>7</sup> for more details) and found that 60% of patient data from the NI trials had never been published before. In their report update, The Cochrane Collaboration showed that there was insufficient evidence that NIs reduced complications of influenza or hospitalisations.<sup>8,9</sup> This event raised the question as to whether stock-piling NIs for flu epidemics in many countries had been an appropriate use of public money (424 million pounds spent alone in the UK)<sup>8</sup> and prompted to seek measures on aiding decision-making in case of incomplete information in the future.

The case of NIs is probably the most well-known example of reporting bias that led to incorrect conclusions on drug effects.

The next example shows the level of detail that needs to be available to provide a meaningful assessment of a given drug. In 2012, the German HTA agency, the Institute for Quality and Efficiency in Health Care

(IQWiG), assessed whether linagliptin had an added benefit over glimepiride, a sulphonylurea, in patients with diabetes.<sup>10</sup> The assessment was based on *Study 1218.20*, published in *The Lancet* in 2012.<sup>11</sup> The study authors stated that in the linagliptin group, hypoglycaemic episodes occurred in fewer patients than in the glimepiride group.<sup>10</sup> This result suggested that linagliptin had an added benefit over glimepiride. Having access to the full CSR of the study, IQWiG was able to peruse the intention-to-treat analysis of the time-course of HbA1c (glycated haemoglobin), which was not available in the publication. They found that there had been a sharp decrease in HbA1c in the glimepiride group (but not in the linagliptin group) in the first 12 weeks of the study. This was probably due to a forced titration of glimepiride as the study aimed for a low blood glucose target. Linagliptin, on the other hand, was given as a fixed-dose treatment without such a target. Examination of the patient data listings of the CSR showed that almost all hypoglycaemic events occurred during this 12-week titration period. Therefore, in contrast to the journal publication, IQWiG concluded that *Study 1218.20* did not provide convincing evidence regarding an added benefit of linagliptin over glimepiride because it could not distinguish between effects of different treatment regimens (fixed dose versus forced titration) or simply, different drugs (linagliptin versus glimepiride, for details see Wieseler 2017).<sup>12</sup> In this case, relying on the publication alone might have led to inappropriate decisions on the use of linagliptin and on its reimbursement price in Germany.

These examples show that the completeness of data available in CSRs is often not adequately reflected in journal publications. In fact, by comparing study results reported in journal publications and study registries with those in CSRs, research showed that the latter provided complete information on a considerably higher proportion of outcomes (86%) than publications and registries combined (39%).<sup>10</sup>

A body of evidence dating back several decades ago demonstrated that reporting bias is a universal problem in medical research.

## CSRs need to be made available

The CSR is a comprehensive document that meets all requirements for valid decisions not



only at regulatory but also at policy-making levels (see “Criteria for valid decision-making in managing health care”). It also offers high-quality reporting, as the structure of CSRs follows standard requirements (ICH E3). CSRs should be disclosed to allow scrutiny: readers should be able to see omission of pre-specified data, data dredging, arbitrary changes to data collection, and other sources of bias.

## Steps to disclosure

Although lack of transparency in clinical trial reporting has been known for decades, countermeasures are being only slowly implemented.

### Study registries

The introduction of study registries was an important step towards the greater goal of full data disclosure of clinical trials. However, recent research has shown that study registration, and perhaps even more so, registration of study results, does not reach the completeness intended by the initiators of these databases. Recent research suggests that a considerable amount of data that should be included in registries is either missing, outdated, or even incorrect. Examples are accuracy of recruitment status and completeness of trial results.<sup>13,14</sup>

### Scientific journals

Data transparency has been a topic in scientific journals for quite some time. Major journals such as the *BMJ* and *PLoS Medicine* require authors to submit entire study protocols together with their manuscripts and publish them as online supplements to the final article.<sup>15,16</sup> In addition, many journals only accept study manuscripts that are registered in a publicly available study registry. However, a recent article in the *BMJ* found that improperly registered studies rejected by the *BMJ* were subsequently almost always published in another journal.<sup>17</sup> Stricter requirements among journals may be implemented. A recent statement of the International Committee of Medical Journal Editors (ICMJE) outlined future conditions for the publication of articles on clinical trials in their journals, making the inclusion of a data sharing statement in the manuscript and a data sharing plan in the trial’s registration mandatory.<sup>18</sup> This policy may further support the goal of full data disclosure, especially with regard to study results.<sup>19</sup>

### Initiatives by regulatory bodies

The fact that comprehensive trial information has been routinely available for regulatory decision-making has led to various initiatives promoting the publication of regulatory data.<sup>20</sup> The EMA

was the first regulatory body to make at least part of the information on a clinical trial available. In 2010 the EMA implemented a policy on access to clinical trial information by request and in 2014 on the pro-active routine publication of clinical data from drug trials (policy 0070).<sup>21</sup> Through this policy, clinical data (including CSRs) for all applications for centrally authorised drugs submitted to the EMA from January 1, 2015, and extension line applications submitted from July 1, 2015, are available to the public (see articles on this issue of *Medical Writing*).

At present, the EMA’s aim to publish all clinical data on new drug applications rapidly has not been fully achieved. The availability of data in the EMA’s database lags behind the rate of new applications. This is probably due to redaction before publication of the data. Manufacturers have the right to redact certain passages in the submitted documents that they classify as CCI. In general, the EMA does not consider CSRs to be CCI and redaction is intended to be limited. It remains to be seen whether and in what way redactions may hinder the scientific usability of CSRs, and whether clinical trial data will be published more swiftly after drug approval.

The FDA is lagging behind its European counterpart. But in a recent press release, the FDA announced a pilot programme, which

started in January 2018, through which CSRs will be released on a new section of the FDA website.<sup>22</sup> Posted information will also include protocols, protocol amendments, and statistical analysis plans. The pilot project will contain up to nine drug applications. If successful, this may lead to the routine release of CSR data on the FDA website for future drug applications.

## Outlook

In light of these developments, one might think that the problems surrounding transparency of clinical trial data are largely solved or are close to being solved. Indeed, there is reason for optimism. Compared with the previous situation, we have seen relevant improvements. Since the case of NIs became public, both the discussion and the measures taken seem to have been accelerated. However, it is still a long way to go. The current initiatives of EMA, FDA, and ICMJE cover only data on new studies of drugs submitted for approval. So far, there is no concept for publishing the CSRs of studies that were conducted before these measures were initiated, even though these CSRs refer to the vast majority of drugs currently used.

For non-pharmaceutical interventions (e.g., medical devices, in vitro diagnostics, etc.), the situation is even more unsatisfactory. Standards for study reporting are less detailed, and clinical trials for all high-risk devices have only recently become mandatory in the EU.<sup>23,24</sup>

Meanwhile, the discussion about data sharing has progressed. The focus has begun to shift from aggregated data (bodies of CSRs and supplementary tables) to the sharing of individual patient data (IPD).<sup>25,26</sup> In its *policy 0070*, the EMA has taken a first step in this direction. The policy plans to make IPD available; however, the discussion on how to achieve this without compromising data protection of study participants has only just started.

Whatever direction further measures will take, CSRs are at the centre of the current development and will remain so. CSRs really matter because they provide a ready-to-use complete representation of a study in the required level of detail and represent the most comprehensive format available for the reporting of the methods and results of clinical trials. CSRs

will therefore be the core element of clinical data sharing for the foreseeable future.

In conclusion, the times when writing CSRs was referred to as purely “regulatory medical writing” are over. CSRs will remain the core documents for drug approval, but their use is extending beyond regulatory activities and beyond being a data source for heavily condensed publications reporting selected data. In the near future, CSRs will be available as information sources for independent researchers and post-approval decision-makers. Therefore, for all

medical writers who write CSRs and wonder who they are writing for, good news is coming: Your reports have gained in importance and will continue to do so, your audience is constantly growing, and your work may be relevant and sought after for years to come.

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## Conflicts of interest

The authors are employed by the Institute for Quality and Efficiency

in Health Care (IQWiG), Cologne, Germany. To produce unbiased HTA reports, the Institute depends on access to all of the relevant data on the topic under investigation. The authors support public access to clinical study reports.

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# CORE Reference (Clarity and Openness in Reporting: E3-based)

– a tool for modern clinical study reports in an era of increasing transparency and disclosure

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## Abstract

CORE Reference ([www.core-reference.org](http://www.core-reference.org)) facilitates the authoring of a content-driven clinical study report (CSR) that is as “public disclosure-ready” as possible. It has potential to increase the quality of final CSRs and enhance consistency within and between sponsors.

The ever-burgeoning regulatory guidance document substructure contains content requirements mandated subsequent to the International Council for Harmonisation (ICH) E3 guidance that must be worked into CSRs; these are integrated into CORE Reference. It is also the only known freely-available resource that pinpoints the sections in an ICH E3-compliant CSR that are potentially affected by public disclosure considerations.

Two years on from its initial release in May 2016, the developers of CORE Reference review the growing utility of this important tool, and place it into the context of the current global era of increasing data transparency and disclosure, where policies and guidelines in development beyond European borders will further mandate carefully authored CSRs for sharing in a global public arena.

## Introduction

Any guidance or reference material reflects requirements at a static time point. The clinical study report (CSR) has its origins in the 1995 International Council for Harmonisation (ICH) regulatory guidance document ICH E3 on the structure and content of CSRs,<sup>1</sup> and the 2012 ICH E3 supplementary Questions & Answers (Q & A).<sup>2</sup> However, modern clinical study designs often integrate pharmacokinetic, pharmacodynamic, pharmacoeconomic and pharmacogenomic elements with a safety and efficacy backbone. To meet today’s complex clinical-regulatory requirements, clinical studies need a fit-for-purpose reporting framework that may differ substantially from that of the more straightforward efficacy and safety studies of 20 years ago, which ICH E3 set out to support. In addition, the ever-burgeoning regulatory guidance document substructure contains additional content requirements that must be worked into CSRs. Even the most experienced and laterally thinking CSR author must be extraordinarily diligent and well informed to keep pace. Specifically, the new area of public disclosure of CSRs, now mandated in the European Union, is worthy of mention. This has profound effects on the way that CSRs must now be written. European Medicines Agency (EMA) guidance on preparing clinical data for public disclosure<sup>3</sup> explains that masking confidential or sensitive information using black-box redaction methods alone will “decrease clinical utility of the data compared to other techniques”, so it strongly encourages the move towards other anonymisation techniques. The impacts on the CSR are multiple and complex, and lessons will be learned as CSRs are disclosed in increasing numbers.

## The global push for data transparency increases potential utility of CORE Reference

Regulators around the world are following EMA’s lead on public disclosure of clinical data. Health



Canada’s draft guidance<sup>4</sup> on public release of clinical information – to support proposed changes<sup>5</sup> to the Food and Drug and Medical Device Regulations – is open for public consultation until June 25, 2018; the US FDA announced plans to publish CSRs in a pilot scheme “...to evaluate whether disclosing certain information included within CSRs following approval of a NDA improves public access to drug approval information.” The plans indicate that the CSR body, protocol and statistical analysis plan will be shared. When the pilot is concluded, CSR portions will be publicly posted.<sup>6</sup>

The (European) General Data Protection Regulation (GDPR)<sup>7</sup> – enforced on May 25, 2018<sup>8</sup> – has far-reaching implications for the safe sharing of clinical trial data. Article 2 states:

The principles of, and rules on the protection of natural persons with regard to the processing of their personal data should, whatever their nationality or residence, respect their fundamental rights and freedoms, in particular their right to the protection of personal data...

Overlaps between regulatory public disclosure requirements and compliance with GDPR will become clearer in the fullness of time.

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As a result of all of the above, CSR authors face increasing challenges of creating CSRs that support heterogeneous study designs, whilst covering all of the important and emergent content requirements, including current and future public disclosure requirements.

### CORE Reference presents focused CSR structure and content addressing current regulatory guidances, including public disclosure

ICH E3 and the 2012 Q & A do not mandate a template order of presentation for design elements, but allow flexibility in structuring the CSR appropriate to individual study design. In the absence of a common approach, a CSR framework for individual studies inevitably results in wide variability in report structures.

CORE Reference ([www.core-reference.org](http://www.core-reference.org)) was developed as an open-access “user manual” to help CSR authors navigate the relevant guidelines so they can create CSRs that are relevant for today’s studies.<sup>9</sup> The ICH E3 Q & A 2012<sup>2</sup> document states unequivocally that ICH E3<sup>1</sup> is a guidance document and not a template. Similarly, CORE Reference is a user manual and not a template. Multiple, extensive and rigorous literature searches were conducted throughout the project to support the broad aim of integrating relevant global and regional (EU and USA) regulatory guidance into the CORE

Reference document. Thus CORE Reference presents a suggested focused structure and content that addresses the current guidance documents and also provides insights and suggestions for anonymisation techniques and approaches that will minimise redaction requirements in the publicly disclosed CSR. CORE Reference is the only known freely-available resource that pinpoints the sections in an ICH E3-compliant CSR that are potentially affected by public disclosure considerations.

To allow easy mapping to the original ICH E3 guidance document and to avoid conflict with guidance documents that refer to ICH E3 sectional numbering, CORE Reference maintains the level 1 heading hierarchy of ICH E3. It remains at the author’s discretion to decide on the most appropriate CSR structure beyond that, although CORE Reference provides some helpful guidance based on the experience of its development team.

### CORE Reference credentials

The CORE Reference manual was created over a two-year period by a group of highly experienced experts in ICH E3, CSR templates, CSR authoring, and the public disclosure of clinical-regulatory documents. These individuals included

The impacts on the CSR are multiple and complex, and lessons will be learned as CSRs are disclosed in increasing numbers.

employees of pharmaceutical companies and contract research organisations, as well as freelancers, who were brought together in an attempt to represent the range of perspectives of professionals commonly engaged in authoring clinical-regulatory documents. A statistician and clinical pharmacologist also joined the team at a later date to ensure that all areas had expert input. The CORE Reference initiative was supported

by the European Medical Writers Association (EMWA) and the American Medical Writers Association (AMWA). It was registered with EQUATOR<sup>10</sup> (Enhancing the QUALity and Transparency Of health Research) Network, which is an international initiative that seeks to improve the reliability and value of published health research literature by promoting transparent and accurate reporting and wider use of robust reporting guidelines. Stakeholders were also involved in the review of the draft CORE Reference document, and included experts from a global industry association, regulatory agency, patient advocate, academic and Principal Investigator representatives.

### Understanding CORE Reference utility

CORE Reference comprises a Preface, followed

by the actual resource. The Preface clarifies intended use and underlying principles that inform resource utility. The Preface lists references contributing to development of the resource, which broadly fall into “regulatory” and “public disclosure” categories. The CORE Reference document includes ICH E3 guidance text, ICH E3 Q & A 2012-derived guidance text and CORE Reference text, distinguished from one another through the use of shading.

All ICH E3 guidance text is either included as original wording; or is included as modified wording and the modification is explained; or is omitted, with the omission being shown and the reason for the omission explained. All ICH E3 Q & A 2012-derived guidance text is included and explained. Rationale comments – in “comment balloon” format on the right-hand side of each page – are used for explanation and clarification purposes. A key explaining text shading and comments is included in the footer of each page of CORE Reference. Where alternative presentations of the same information would work equally well in a CSR, they are shown with an explanation provided in the Rationale comments to allow CSR authors to make informed authoring choices relevant for their particular study. A separate mapping tool comparing ICH E3 sectional structure and CORE Reference sectional structure is also provided. Together, CORE Reference and the mapping tool constitute the user manual. CORE Reference is provided as a PDF. The separate mapping tool is provided in spreadsheet format to support its utility.

It is important to note that CORE Reference was developed using a proactive approach to the complex area of CSR disclosure since it was observed that the pharmaceutical industry was

developing a two-step process for submitting and then publishing clinical study results. This two-step process involves producing a submission-ready CSR that may contain sensitive data that must be removed after submission to produce the final disclosure-ready CSR. The “primary use CSR” (the EMA term is scientific review version)<sup>3</sup> is a technical document for regulatory review and comprises full CSR text and all CSR appendices. The “secondary use CSR” (the EMA term is redacted clinical report)<sup>3</sup> is for public disclosure and comprises redacted CSR text and

selected appendices. Sensitive information presented in the primary use CSR is redacted in the secondary use CSR. CORE Reference proposes that the CSR should be as disclosure-ready as possible from the outset to safeguard against inadvertent identification of participants or commercially confidential information, assure optimally timed public disclosure of clinical trial

results, and be as cost efficient as possible. The latest available guidance on public disclosure of clinical-regulatory documents has been integrated into CORE Reference through discrete colour-coded comments prompting the user to consider both the primary and secondary use CSR. These guidance comments incorporated into CORE Reference should help CSR authors make informed choices as they navigate the evolving and complex area of redaction of sensitive information prior to public disclosure.

### Growing awareness

CORE Reference has been actively taken up within pharmaceutical companies and contract research organisations (CROs), with over 12,000 downloads of CORE Reference and over 5,600 downloads of the mapping tool between May 2016 and May 2018). Several organisations have adapted it into a template for use with their standard operating procedures (SOPs). With sufficient uptake,

With sufficient uptake, it has potential to drive standardisation of the writing of CSRs across the industry.

it has potential to drive standardisation of the writing of CSRs across the industry.

Of course, any resource can only remain relevant if it is updated on an as-needed basis. This is a stated aim for CORE Reference.<sup>9</sup> Some 4 months after CORE Reference was launched, the US Department of Health and Human Services published the Final Rule on clinical trials registration and results information sharing,<sup>11</sup> effective January 18, 2017, which mandates the registration and submission of summary results from clinical trial results information in [clinicaltrials.gov](http://www.clinicaltrials.gov) ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) for certain clinical trials of drugs (including biologic products) and devices. Although the detailed requirements will not impact results reporting in CSRs *per se*, signposting to these requirements (as already done for similar EudraCT results posting requirements) in a future version of CORE Reference is expected to add tangible value for sponsors in managing registry postings alongside the writing of CSR results content. Ongoing due diligence of the evolving regulatory landscape will also support future updates of CORE Reference.

In summary, CORE Reference facilitates the authoring of a content-driven CSR that is as disclosure-ready as possible. It should also increase the quality of final CSRs and enhance consistency within and between sponsors. It may also benefit systematic reviewers in their use of CSRs and provide a useful resource for auditors on all the current guidance documents associated with a CSR. The CORE Reference website ([www.core-reference.org](http://www.core-reference.org)) also supports sharing of feedback, as well as providing regular news updates after sign up at <http://www.core-reference.org/subscribe>. The website is a living resource that archives CORE Reference-related print publications and audio-visual media following live presentations. A “Coming Soon” section supports educational planning needs.

### Conflicts of interest

Both authors are freelance medical writers and have no conflicts of interest to declare.

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### CORE Reference is a user manual and not a template.

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With over 30 years in pharmaceutical and CRO environments, **Debbie Jordan** set up a medical writing group in a large CRO, growing her 7-strong team over 4 years, before establishing her own freelance medical writing and clinical research service enterprise. Debbie was a key member of the CORE Reference development team.



# Preparing clinical study reports for external sharing

how to balance patient privacy/  
data utility priorities and manage risk

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## Abstract

As the EMA refines its requirements for the external publishing of clinical study reports, the workload of medical writing teams is increasing to include robust processes for clinical study report anonymisation. Until now, life sciences firms have played this safe by using heavy content redaction (covering up identifying information with a blue box), but now EMA is encouraging anonymisation over redaction to help maximise data utility while simultaneously mitigating the risk of patient identification. (Anonymisation involves changing identifiers, but they are still readable, such as placing an age of 27 into a band of 20–29). This article explores the issues and considers companies' options.

EU measures to make clinical trial data open for public access have created substantial additional work for medical writers and transparency departments. In line with general shift towards greater transparency, companies must now tread a careful line between maximising the utility of clinical trial information and safeguarding patient identities as study reports are shared more widely.

Under EMA Policy 0070 on the publication of clinical study reports (CSRs) relating to medicinal products for human use, CSRs must be anonymised to prevent patients (and indeed professionals) who participated in clinical trials from being identified. The standard approach has been to redact anything that might identify an individual by using Adobe Acrobat software to cover that text with a blue box bearing the letters PPD for "protection of personal data". In a supporting anonymisation report, the writing team explains what they have covered up and why.

There are several problems with this approach to patient risk management. The first is that it places a significant additional administrative burden on medical writers. Anonymisation via manual redaction is a labour-intensive process, taking up a considerable amount of trained experts' valuable time – given that CSRs can run from between 5000 to 100,000 pages – and sometimes even more. Second, it carries a risk. If just one potential subject identifier is missed, it would be quite easy for someone to piece together more specifics about the study – details which, in line with EU requirements, should not be disclosed outside of the immediate R&D team. A third significant issue is the impact of heavy redaction on the residual value of the amended content to interested external parties. If the goal is to make CSRs more open and available for external scrutiny, that aim is immediately compromised as soon as large sections of those reports are covered.

### Smart approaches to identity safeguarding

It is this issue of clinical trials' external utility that has prompted new efforts by the EMA to dissuade life sciences R&D organisations from relying on redaction as their method of choice for report anonymisation. Instead of a very conservative “cover all” approach, EMA advocates that companies anonymise externally facing reports by using anonymisation techniques that can be adapted according to the perceived level of risk of patients being re-identified.

Using techniques such as date offsetting (assigning a random number to a patient and then changing all the dates related to that patient by this number) and other systematic (and internally traceable) alterations to identifiers, companies can confidently disguise revealing information while retaining the integrity of the findings and the surrounding narratives. An added benefit is that if an occasional identifier is missed, there would be nothing to suggest to the reader that it was a real clue regarding the original data; effectively, it would be hiding in plain sight. As a result, there is much less risk with this approach to the safeguarding of patient privacy.

### Improving data utility through more accurate risk measurement

EMA has defined the acceptable risk level for



patient re-identification to be 0.09 – meaning that each subject's defining characteristics (country of residence, race, etc.) must be in common with those of at least 11 other patients taking part in the trial. One option if this is not the case is to anonymise data in a way that creates larger groups or equivalent classes – e.g., using “European” in place of “Irish”, or “other” for non-white ethnicity in a group with too few black or Asian subjects. Another option is to include subjects from other trials within the same therapeutic area within the same geographic area. This involves creating a larger population from which you are going to calculate your risk metrics. For example, if a sponsor is conducting several cancer trials within a given period, that information can be leveraged to help create a larger population on which you calculate risk. This is common practice when anonymising small trials.

The great advantage of this type of systematic approach is that information technology systems can take over much of the process, requiring only quality assurance checks from medical writing teams. Busy professionals are saved from doing all the legwork but they retain control over risk management. Systematic anonymisation is also much easier to audit internally, so teams can keep track of what they have done. They also will have a record of their actions, which they can use to demonstrate that all possible steps were taken to

protect the identity of patients.

One of the inhibitors to this kind of initiative has been a lack of drive from the EMA to make things happen, despite the agency's best intentions. To date, it has offered just guidance. Up to now, therefore, the majority of firms have continued to default to redaction, relying on outsourced services to fulfil the requirement if internal medical writing teams have not had the capacity. While not the most efficient and reliable approach, it has been seen as the least disruptive.

To continue in this vein is short-sighted, however. Other regions including North America and parts of Asia are already taking active steps towards anonymisation of clinical findings. Health Canada has already made in-roads with a very similar approach to EMA's, the FDA is likely to be next, and Japan is taking decisive steps too. The future will likely see a shift towards anonymisation, quantitative risk measurement and a focus on data utility. Whether guidance becomes law remains to be seen.

### Going deeper: Anonymising underlying patient data sets

Although talk of the EMA extending its anonymisation requirements to individual patient data – i.e., underlying trial data sets – has not yet come to anything, it is an approach that offers maximum efficiency for the long term. Ben Rotz, director of medical transparency at Eli Lilly,

said at a recent conference that he did not expect Phase 2 of EMA Policy 0070 (data-level requirements) to be introduced in the next 10 years. But this does not take away from the process streamlining that is enabled by applying anonymisation techniques at the core. For one thing, it is the best way to get to an accurate risk score (enabling a quantitative rather than merely a qualitative risk measure). There are signs that some companies have recognised this, seeing the merits of linking documents to original data sets more dynamically.

Industry leaders are starting to apply more automated anonymisation methods to their CSRs, seeing the value in a more systematic approach. An added benefit is that associated anonymisation reports can be generated automatically, saving medical writing teams a lot of time and ensuring that nothing is left out in the explanatory notes.

These trailblazers are not doing this to score points but rather to reduce workload and to increase the consistency and value of their output. Although the EMA is still accepting any form of anonymisation, including redacted clinical reports, ultimately it is life sciences organisations that will suffer the consequences if a patient is re-identified because of inadequate risk processes.

Firms are now faced with maximising the utility of their data to external audiences while limiting the risk that individual patients will be identified. Systematic approaches to data-level anonymisation techniques offer the most flexible way to meet both goals. One of the outstanding issues to date has been that the EMA has not been very clear about the target audience for externally published report content. If it is the general public (e.g., interested patients), they are unlikely to understand the detail and language used in CSRs, so the value is questionable. If the audience is other researchers, it

could be argued that a summary and details of efficacy and adverse events would suffice. But interestingly, of the parties seen to access shared content to date, the largest audience has been other pharmaceutical companies – their main

driver for accessing the reports being to understand how their peers are approaching document anonymisation. Yet, as an educational resource on anonymisation, the current population of reports are not great examples of high-quality anonymisation combined with accurate risk metrics. There is plenty to improve upon.

### Leading on data transparency: Pharma's time to shine

For now, progress depends on life sciences companies being able to see the bigger picture and appreciate the business benefits they can derive from being (a) more open and transparent with the market, and (b) more systematic and efficient in the way they manage personal data protection and risk.

Something to bear in mind is how quickly technology is developing and growing in sophistication, especially in the context of artificial intelligence (AI) and machine learning. Incorporating automated intelligence within anonymisation applications offers teams the ability to teach systems to more accurately recognise potentially sensitive references, links, and context – and to take specific action (e.g., offset all associated dates by X days), or flag them to the teams for checking. Intelligent software can pick up inconsistently spelled references, which a text search might miss.

Initial benchmarks suggest that by the seventh time a system has been shown something (e.g., what constitutes a sensitive identifier), it is already at human-level accuracy. After that, it soars ahead, becoming progressively better and faster. So productivity increases and leak rates (mentions being missed) drop significantly – to a level less than 1%. AI-based systems can also be set to apply different levels of risk mitigation – so if there are sensitivities about alcohol use or pregnancy, for example, anonymisation actions can be set accordingly.

But of course technology alone does not have all the answers. Organisationally, there are still communication gaps among medical writing,

privacy, and data teams, and between internal departments and outsourced service providers. These barriers, added to an unwillingness to take investments beyond the scope of basic compliance, will limit what companies are able to achieve – unless they proactively take steps to change things.

For patients' sake, it is essential that life sciences organisations are vigilant about protecting patient privacy and about regularly reviewing the risks of re-identification. In the interests of keeping pace with the way authorities' requirements are going, it is far better that companies move forward with higher goals now than remain behind the curve as the industry presses on with plans for greater transparency and collaboration.

An insightful observation made at an event recently was that while all sorts of companies, from banks to internet companies, are pulling out all the stops to collect data, very few are sharing it for the greater good. The pharma industry might be slow to adopt other technology trends, but it is taking a lead in data transparency. Make the right choices now and in 10 to 15 years' time companies could find themselves giving advice to businesses in other sectors about best practice strategies and describing how they got to where they are.

### Disclaimer

The opinions expressed in this article are the author's own.

### Conflicts of interest

The author is employed by d-Wise Technologies, a specialist provider of data and process optimisation services for life sciences and healthcare industries.

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An insightful observation made at an event recently was that while all sorts of companies, from banks to internet companies, are pulling out all the stops to collect data, very few are sharing it for the greater good.



# Harmonising format and style requirements for scientific and medical publications: Time to address a long-pending dream

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## Abstract

Scientific and medical publications are the pulse of the clinical world and play a key role in disseminating data to healthcare providers, scientists, and researchers. However, the process of publishing is hampered by the lack of harmonisation in structure, format, and style of manuscripts across journals. The authors/writers are challenged by this variability, which dilutes their ability to focus on science and medicine. The key challenges of structure, format, and style, including word count, referencing, and citation, are discussed here. We also provide a framework for a possible solution. We urge key stakeholders to come together and harmonise the formatting and technical requirements of scientific and medical publications with consensus from pharmaceutical industry, academics, publishers, and relevant organisations with expertise in medical writing and publication planning. It would take considerable effort from all stakeholders, but the end result of harmonised specifications represents a “blue sky” that is worth striving toward.



## Introduction

Scientific publications have long shown great variability in presentation styles, and readers have thoroughly enjoyed it. Nevertheless, as the number of publications increases year after year, this variability now can seem tormenting to researchers, authors, writers, and editors who frequently find themselves revising text and figures to meet the requirements of different journals or research conferences. As a major reform, we have harmonised the structure and content of regulatory documents used in clinical research. Scientific publications, however, have not received the same attention. Publications lag behind largely due to the lack of consensus and wide variation in audience. We

understand that journals have different missions and that there is considerable variability in the points of view of editors regarding how to present information. Nonetheless, we would like to assert that such variability drains time and resources and imposes a barrier to the timely presentation of data.

Thus, we propose that it would be worthwhile to harmonise scientific publications similar to what has been done for clinical study reports (CSRs) through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Many times good data gets rejected because of formatting, styling, and structure. Manuscripts often must be submitted to multiple journals before being accepted, resulting in the need to follow different guidelines

and formatting styles. The International Committee of Medical Journal Editors (ICMJE) has been working hard to improve the quality of reporting and publishing the clinical trial results. Keeping this in view, we urge the ICMJE, perhaps in collaboration with ICH and the International Society for Medical Publication Professionals (ISMPP), to consider, implement, and mandate the harmonisation across scientific publications, at least the style and the format.

The current article discusses the emergent need of harmonising scientific publications in journals and conference presentations. This article additionally discusses the existing publication guidelines and suggests amendments that might help in harmonisation of publications. This might help writers, researchers, and authors focus on science rather than editing, formatting, and styling aspects. This would also address the gap in time between a novel finding and the dissemination of this information, which is often critical for patient health and the public's good faith in clinical research. Many times good data gets rejected because of formatting, styling, and structure.<sup>1</sup> This clearly indicates the emergent need of harmonising the scientific publications.

### Guidelines, recommendations, and lacunae

Currently, no guidelines exist that ensure harmony within journal publications and conference presentations across the globe.

Guidelines issued by the ICMJE and American Medical Association (AMA Manual of Style) are the most followed ones, but these do not cover aspects such as harmonised structure and format, though they have made some recommendations. To add to it, ICMJE does not mandate that these recommendations be followed. Consequently, the authors and writers are often challenged with these petty issues, which heavily affect time, cost, and resources, especially when a publication is being resubmitted or re-purposed. This section provides an overview of recommendations by ICMJE and AMA Manual of Style.

#### ICMJE

The ICMJE is a non-profit group comprising general medical journal editors and representatives from selected organisations and aims to improve the quality of publications while complying with publication ethics. The ICMJE has developed recommendations that cover best practice and ethical standards for conducting studies and reporting results.

Regarding manuscripts, the ICMJE has recommended the use of a document format commonly referred to as IMRAD for the major sections within the manuscript structure – for Introduction, Methods, Results, and Discussion. It is a de facto standard for most manuscripts and even abstracts.<sup>2</sup> The ICMJE has also provided recommendations for title page, abstract, and

references.<sup>3</sup> The ICMJE journals follow these guidelines, which creates harmony within this group of journals. Furthermore, there is also a standard format for reporting conflict of interest (COI). However, it should be noted that many other journals do not abide by these recommendations.

#### AMA Manual of Style

The *American Medical Association Manual of Style* aims to guide writers regarding manuscript preparation, referencing, and data presentation, and it also serves as an editorial style guide. The content is very helpful, but as with the limitation with ICMJE, some journals do not follow the AMA style guide and have their own formatting and styling guidelines.

In the following sections, we will discuss the challenges, and we offer solutions that may help to streamline the publication process.

### The array of challenges in publications

Before taking a plunge into the solutions, it would be helpful to understand the array of challenges while developing and resubmitting scientific publications. With a goal of setting priorities and providing a framework for creating solutions, we rank the challenges by the extent of their impact. The key challenges in authoring and re-purposing publications are presented in Figure 1.

1. Referencing and citation	2. Word count	3. Illustrations	4. Structure and style
<ul style="list-style-type: none"> <li>● Limit on the number of authors</li> <li>● Bold or italic letters</li> <li>● Placement of year – after authors or journal</li> <li>● Requirements to use or omit commas and periods when listing author names</li> <li>● In-text citation using superscripted numbers, in-bracket numbers, or author, year, etc.</li> </ul>	<ul style="list-style-type: none"> <li>● Number of words in abstract, manuscript by type, e.g. systematic review, meta-analysis, etc.</li> <li>● Words/character count across congresses for the abstracts</li> <li>● Acknowledgements, disclosures, and other such sections should not be included in allowed word count.</li> </ul>	<ul style="list-style-type: none"> <li>● Differences in numbers of tables and figures permitted</li> <li>● Supplementary illustrations not always permitted</li> <li>● Colour illustrations not always permitted or affordable, sometimes resulting in need to redraft figures to avoid difficult-to-read greyscale images</li> <li>● Technical challenges in creating figures/images according to journal format</li> </ul>	<ul style="list-style-type: none"> <li>● Lack of harmonisation in overall manuscript structure requirements (IMRAD or not; varying specifications about review)</li> <li>● Differences in headings/sections to include in abstracts</li> <li>● Presentation style for conference abstracts, e.g., landscape or portrait</li> </ul>

Figure 1. The top four challenges in authoring and repurposing publications

**Challenge 1: References and citation**

On the top in the list is referencing, which has the maximum impact, not only in terms of formatting and styling but also for citation in text. This variability in reference format and style might be found in journals belonging to same publisher as well. This is one of the dreariest tasks that authors and writers face, especially while resubmitting. The style variation is huge, e.g., how many author names to list before using *et al.*, where to place the year of publication, whether or not to italicise or abbreviate the journal name, whether or not to place the volume number in bold, how many references may be included, etc. Similarly, citation within the text is also highly variable – whether to use superscripted numbers, author-year, and bracketed, etc. Redoing citation style and renumbering the references is a marathon task, prone to errors, and becomes challenging with each resubmission of a manuscript to a new journal.

Software such as EndNote, Reference Manager, and Zotero are available for referencing, and work as fast as a click of the mouse, but full and efficient versions can cost somewhere around US\$200, though student and institutional discounts may be available. License renewals and upgrades result in additional costs.

**Challenge 2: Word count**

A second important challenge is word count limits. It can be especially annoying to have to reduce the word count in a draft that has already been approved by the author team. Word limits can affect both the abstract and the text as a whole. For the abstract, a limit of 250 to 300 words seems to be appropriate because a lower limit may be inadequate for conveying a comprehensive summary of the study, especially for complicated studies. Similarly, a 1,500 word count for the manuscript could be constraining

– at least until we adopt the idea of “lean publications” and limit the introduction and discussion to the essential points, the methods to provide enough reproducibility, and results to the key findings and described in a tabular format. In a previous article, we suggested a framework to keep publications “lean and mean”, i.e., short and to-the-point.<sup>4</sup> If implemented, this would keep many of the word count challenges at bay.

Another point of discussion that comes to mind is whether journals and conferences should use word count or character count as the preferred method of restricting length. The character count may seem attractive because it would force the use of shorter words instead of longer/fuzzy words, but it may complicate scientific writing. Limiting by character count introduces the need for engaging in extra shortening efforts, such as creating unfamiliar and difficult to remember abbreviations/short forms, which might reduce the readability of the text. Character count limits are often found in requirements for conference abstract submissions; these limits become particularly problematic when authors are uploading their abstracts to submission websites. There is often a mismatch between how software programs such as Microsoft Word count characters and how conference websites count them. Authors/writers then must struggle with last-minute adjustments to text.

Another factor that needs discussion here is whether the word/character limits include acknowledgements, disclosure statements, and other non-technical sections. Standardisation in this regard also needs to be addressed.

It can take arduous efforts to modify a manuscript to reduce the word count. For industry publications, multiple stakeholders are involved in the review process, making the process of re-drafting, re-reviewing, and re-

approving quite sluggish. This ultimately undermines the whole purpose of publications, i.e., disseminating results to the healthcare and research professionals at the earliest to extend the treatment benefit.

**Challenge 3: Number of illustrations**

Illustrations (figures, tables, and images) are the backbone of any scientific publication. They efficiently convey the results to the intended audience. Figures often take considerable effort to generate. Journals often recommend six illustrations, but there is a large variability. Resubmitting a manuscript to another journal that allows fewer illustrations can be overwhelming, especially if journals do not permit supplementary illustrations. The authors and writers need to brainstorm how to eliminate some figures or revise others. This adversely affects the turnaround-time of the manuscript while figures are redrawn, reviewed, and approved. Additionally, there could be figure formatting challenges involving the use of colour or grey-scale, which typefaces to use, etc.

**Challenge 4: Structure, format, and style**

The overall structure of the manuscript is currently the aspect most in sync across journals, as most publications use an IMRAD format. This is also the format recommended by the ICMJE, and it is religiously followed by member journals. Nevertheless, there is variability. Some journals require that results and discussion be merged, while others have a non-IMRAD structure. For abstracts also, sections vary across journals, and some ask for even minor details such as setting, design, etc., to be included under separate headings while others would group these under methods. Review articles, however, may not strictly follow this structure, and requirements about which headings to use vary.

**Table 1. The current publication environment and "blue sky" future**

Aspects	Current	Future
<b>Structure</b>	Variable, exhaustive, and comprehensive	Harmonised, template based, and lean
<b>Format and style</b>	variable	Harmonised, guideline based
<b>Publication</b>	Online as well as in print	Online only, cloud-based
<b>Accessibility</b>	Open and closed access, infrequent use of QR codes	Open access only, mandated use of QR codes
<b>Storage and archival</b>	Individual journal/publication house sites	Common cloud-based storage
<b>Circulation</b>	Infrequent use of digital methods	Use of mobile applications and social media
<b>Publication houses</b>	Multiple speciality journals	Unify by speciality and mergers like pharmaceutical companies

Proposed Manuscript Structure (Template)		Proposed Format and Style	
<p><b>Abstract</b></p> <ul style="list-style-type: none"> <li>● Background, methods, results, and conclusion</li> </ul> <p><b>Introduction</b></p> <ul style="list-style-type: none"> <li>● Background, lacunae, and hypotheses</li> <li>● Study objectives</li> </ul> <p><b>Methods</b></p> <ul style="list-style-type: none"> <li>● Include study design, participants (eligibility, sample size), study endpoints and their assessment</li> <li>● Statistical analysis</li> <li>● Ethical considerations and NCT number</li> </ul>	<p><b>Results</b></p> <ul style="list-style-type: none"> <li>● Primary and secondary efficacy analysis data</li> <li>● Safety data</li> </ul> <p><b>Discussion</b></p> <ul style="list-style-type: none"> <li>● Key findings and discussion vis-à-vis other studies</li> </ul> <p><b>Take home message</b></p> <ul style="list-style-type: none"> <li>● Key points for professionals</li> <li>● Key points for patients and public</li> </ul>	<p><b>Word count limit</b></p> <ul style="list-style-type: none"> <li>● Manuscript body, IMRAD, 2500 to 3000 words</li> <li>● Abstract, 250–300 words</li> <li>● Illustrations, up to 8</li> <li>● Supplementary material, up to 5 files</li> </ul> <p><b>Referencing</b></p> <ul style="list-style-type: none"> <li>● References, up to 45</li> <li>● Citation in text: Author, date or use only PubMed ID, which shows the author, year when mouse is hovered over the ID; use of hyperlinks</li> <li>● Reference format: Vancouver</li> <li>● Reference list: alphabetically or by PubMed ID, as appropriate</li> </ul>	<p><b>Style and formatting</b></p> <ul style="list-style-type: none"> <li>● Follow AMA style</li> <li>● Times New Roman, 12 points, left aligned, double spaced, numbered pages and line numbers</li> <li>● Illustrations cited using Roman numerals</li> </ul>

Figure 2. A framework for harmonising manuscript structure, format, and style

Regarding format and style, again there is tremendous variability. There may be different recommendations for font, line spacing, page setup, page numbering, raised (midline) periods to denote decimals, and number of places after decimals. The list is unending. Illustrations are also affected with formatting and styling issues, and the desired submission file format may be EPS, JPEG, TIFF, or PDF. These varying requirements confuse and overwhelm the authors/writers, and inadvertently choke the publication process. In addition, some journals have started asking for social media messages while some also require take-home message for the patients in simple language. Interestingly, many such requirements are not clearly mentioned in the instructions for the authors provided by the journals, and come as surprise while submitting the manuscripts.

Often, copyeditors are deployed to address these styling and editorial requirements, which is a time, cost, and resource sapping activity. Though it is less likely that manuscript is rejected due to non-compliance with the recommended style guide, it still hampers the publication process and delays publications. This clearly underlines the need of harmonisation, especially

in terms of formatting and styling.

## Solutions

### Harmonised template

Creating a harmonised template would be a milestone in the domain and would help in streamlining the publication writing process. It is important and also worthwhile to harmonise the structure of manuscripts and implement this globally. This would help authors and writers focus on technical scientific/medical content rather than struggle with the formatting and styling issues. We strongly urge ICMJE, AMA, ISMPP, EMWA, AMWA, and publishers to come together and have a consensus on the template. This would also help authors because they could choose a relevant journal based on technical content rather than the allowed amount of text and illustrations. We propose a framework as in Figure 2. The template with guidance or sample text can be issued, though flexibility should be given as with ICH E3 template for CSRs. Regarding the formatting and styling, these too can be recommended/mandated so that manuscripts can be submitted to any journals without any hassles to reduce word count or change format and style.

Another very important effort would be to harmonise the structure and especially the layout of posters. Presenters at conferences print their posters and present at conferences. They might often present this data at another conference with a different audience and might need to print another poster as the conference specifications may differ. Harmonising the poster structure, format, and layout may help in using and reusing the same poster, which may also help in conserving natural resources. In situations where a change is needed to the sequence of authors and title based upon conference region, audience, and presenting author, this information can be added as a sticky note, rather than reprinting the poster again.

### Uniformity in format and styling

Until we reach a consensus on the template, it will be of utmost importance to harmonise format and style, particularly the reference citation, as proposed in Figure 2. We see this as the most important issue and view it as a bottleneck in the already complicated and sluggish publication process that sometimes takes up to a year to print.

Journals and publication houses should come to a consensus with using superscripted numbers,

number in brackets, or author, year styles for citation in text. For the reference list, a consensus of Harvard or Vancouver style may be reached. In summary, whatever is the chosen format and style, it should be implemented globally. We would recommend using an author-year format because it eliminates the challenges encountered with numbering.

### “Your paper, your way”

One very attractive option that we have come across is the “Your Paper, Your Way” initiative of Elsevier journals.<sup>5</sup> Authors can submit the paper as one combined PDF file then apply style and formatting later upon acceptance. Such initiatives are very welcome and will accelerate the publications on one hand and provide relief to the authors who would not have to fear rejection due to failing on these criteria. The only challenge here is the effort in formatting of the manuscript post-acceptance, which may involve adhering to word and illustration limits, changes to reference style, etc.

### Auto-transfer of content from one journal to another

The ability to automatically transfer of manuscripts from one journal to another is another nice initiative by publishers. The journals published by the same publication house have harmony within, and the manuscripts can be transferred using a single click from one journal to another belonging to the same publication house. However, the journals are not essentially the specialty-specific, and may not be the preferred choice/option for the authors or lack a region-specific circulation. Nevertheless, it does address the challenges in formatting and restyling.

### The way forward

In our opinion, the best way forward would be to “lean” publications, and to provide a template format with specifications that is used globally. The “blue sky” is to link the already available information in the public domain, and present the interpretation. For example, the publication could link to the methods disclosed in the protocol, to tables/figures to data in clinical trial registries, and in disclosed CSRs.

Furthermore, template-based writing seems promising in publications, and a benefit similar to that in regulatory writing is expected from this

change. Similarly, for referencing, the recommendation could be to use PubMed IDs, where hovering of the mouse indicates the author, journal, and year. This option is available for most free-full text online papers in an HTML format.

We firmly believe that the printed paper journals will soon become obsolete. Digital is in, and it reduces space constraints of the printed page. We, as authors/writers and publishers should welcome cloud-based publishing with an open mind, and lead the change rather than follow the change. Harmonising publication specifications and moving toward lean publications is the need of the time and in the best interest of dissemination of scientific and clinical data/information. Taken together, there is a lot to implement in future vs. current and reach the blue sky (Table 1), which would help us to realise the long-pending dream of harmonising publications.

### Take-home message

In summary, harmonisation and lean writing is going to be the backbone of publications and will only be realised with efforts from all the stakeholders, including authors, writers, sponsors, and journal publishers, as well as organisations including EMWA, ICH, ICMJE, AMA, the International Society for Medical Publication Professionals, and the American Medical Writers Association. The authors and writers should embrace this idea and journals and publisher should be willing to implement these changes while keeping common interests in mind. In addition, further digitising the publication industry will open new avenues for science and medicine by ensuring wider and more timely and cost-effective reach to the desired audience.

### Conflicts of interest

The authors declare no conflicts of the interest.

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# News from the EMA

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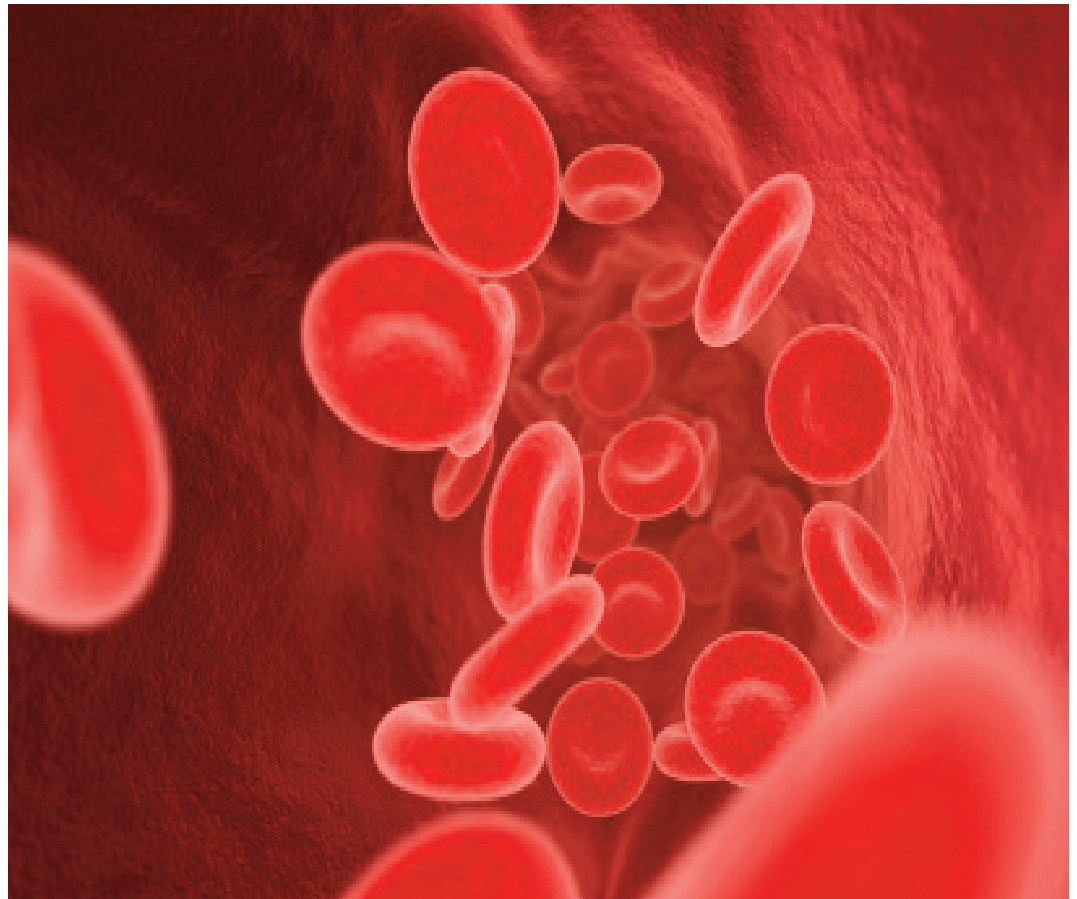
The articles included in this section are a selection from the European Medicines Agency's News and Press Release archive from January 2018 to March 2018. More information can be found on the agency's website: [www.ema.europa.eu](http://www.ema.europa.eu)

## First-in-class medicine to prevent bleeding in haemophilia A patients with inhibitors

**January 26, 2018** – The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorisation for Hemlibra (emicizumab), a first-in-class medicine to prevent bleeding or reduce the frequency of bleeding episodes in patients with haemophilia A with factor VIII inhibitors, in patients of all ages.

Haemophilia A is an inherited bleeding disorder caused by lack of a clotting protein called factor VIII, and affects mainly males. Patients with haemophilia A are usually treated with factor VIII medicines, which replace the missing factor VIII and help control and prevent bleeding. However the body may develop inhibitors (antibodies) as a reaction to these medicines. The inhibitors reduce the medicines' effect, so bleeding is no longer controlled. The development of inhibitors is the most severe treatment-related complication of haemophilia A because it makes it difficult to manage the disease. Current treatment alternatives in patients with haemophilia A who develop inhibitors are time-consuming and often burdensome, particularly for children, and they are not effective in all patients. There is therefore an unmet medical need for more convenient and effective treatment options.

Hemlibra is the first monoclonal antibody to be recommended for use in patients with haemophilia A with inhibitors, an area of medicine where no new medicines have been made available in 20 years. It works by mimicking the coagulation function of factor VIII. The treatment is given weekly via a subcutaneous injection, making it more convenient than bypassing agents (medicines that bypass



factor VIII) which are the current standard of care but which require frequent, prolonged administration by infusion (drip). The Committee for Medicinal Products for Human Use reviewed the application for Hemlibra under its accelerated assessment procedure, which allows the speeding up of patients' access to medicines that address unmet medical needs.

The safety and efficacy of the medicine was evaluated in two phase III clinical trials: a randomised, open-label study conducted in 109 patients aged 12 years or older, and an ongoing single-arm, open-label study in children under 12 years of age, for which results in 60 patients were included in the application. Overall, the prophylactic use of emicizumab in

haemophilia A patients with inhibitors reduced bleeding episodes that needed treatment with coagulation factors by around 80% to 90% compared to on-demand use of bypassing agents without prophylactic treatment.

The most common adverse events observed were reactions at the site of injection, headache, thrombotic microangiopathy (damage to small blood vessels supplying organs such as the kidney), fever, diarrhoea, and joint and muscle pain.

The opinion adopted by the CHMP is an intermediary step on Hemlibra's path to patient access. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation.

## General Court confirms EMA approach to transparency

**February 6, 2018** – The General Court delivered today three landmark rulings for the EMA, upholding EMA's decisions to release documents requested in accordance with Regulation (EC) No 1049/2001, the so-called "Transparency Regulation". This is the first time that the Court of Justice of the European Union (EU) has had the opportunity to pronounce itself on the application of the Transparency Regulation to documents held by EMA.

The judgments concern Case T-235/15, *Pari Pharma v EMA*, in relation to the disclosure of similarity and superiority reports on an orphan medicine, prepared by the CHMP; Case T-718/15, *PTC Therapeutics*

*International v EMA*, on the disclosure of a clinical study report; and Case T-729/15, *MSD Animal Health Innovation and Intervet international*, regarding five toxicology study reports for a veterinary medicine. In all three cases, the pharmaceutical companies challenged EMA's decision to release the concerned documents in accordance with the Transparency Regulation and EMA's 2010 policy on access to documents (Policy 0043).

The General Court noted that the companies failed to give any concrete evidence of how the release of the contested documents would undermine their commercial interests, and therefore it rejected their claims.



Based on the guidance issued today by the General Court, the Agency will continue to diligently assess each individual request for access to documents submitted under the Transparency Regulation and in accordance with its policy on access to documents.

## First medicine to treat neonatal diabetes

**February 23, 2018** – The EMA's CHMP has recommended granting a marketing authorisation in the EU for Amglicia (glibenclamide), a medicine indicated for the treatment of neonatal diabetes mellitus, for use in newborns, infants, and children.

Neonatal diabetes is an extremely rare form of diabetes that is diagnosed in the first six months of life. It is life-threatening and debilitating because of the symptoms caused by high blood sugar levels and the risk of ketoacidosis, a serious problem that can occur in people with diabetes if their body starts to run out of insulin and ketones build up in the body. Different gene mutations have been identified causing this type of diabetes.

Amglicia is a new oral formulation of glibenclamide, a medicine which is already authorised for treating type 2 diabetes, specifically developed for use in newborns, toddlers, and

children with neonatal diabetes. It works on insulin-producing cells in the pancreas by attaching to an ATP-sensitive potassium (KATP) channel, which controls the release of insulin. In many newborn babies with neonatal diabetes, the cells in the pancreas produce insulin but they are not able to release it into the blood because their gene mutations lead to dysfunctional KATP channels. The lack of insulin in the blood causes symptoms of diabetes. Glibenclamide's effect on the KATP channel restores the cells' ability to release insulin into the blood. These effects are expected to reduce the symptoms of neonatal diabetes.

Currently, to treat neonatal diabetes, nursing staff under medical prescription, or the parents at home, administer insulin or off-label commercially-available glibenclamide tablets licensed for adults only. To make the products suitable for

newborns and children, the tablets are crushed into small pieces that are mixed with a small amount of water, and then administered with an oral syringe. This practice can cause errors in the administration, potentially leading to a risk of under- or over-dosing. Amglicia's formulation is meant to allow a more accurate dosing of glibenclamide. Moreover, patients treated with Amglicia may not need to be treated with insulin or may need a smaller dosage.

Amglicia is a hybrid medicine of Daonil which has been authorised in the EU since January 1969. Hybrid applications rely in part on the results of pre-clinical tests and clinical trials for a reference product, and in part on new data. The benefits of Amglicia are supported by data published in literature as well as data from a bio-availability study and the NEOGLI study. Due to the extreme rarity of the disease, there were only 10 patients included in the NEOGLI study. It showed that glycaemic control remained stable after switching from crushed tablets to oral suspension.

Because neonatal diabetes mellitus is a very rare disease, Amglicia was granted an orphan designation in January 2016. As always at time of approval, this orphan designation will now be reviewed by EMA's Committee for Orphan Medicinal Products (COMP) to determine whether the information available to date allows maintaining Amglicia's orphan status and granting this medicine ten years of market exclusivity. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation.



## Revised guideline on clinical studies for Alzheimer's disease medicines

**February 28, 2018** – The EMA's CHMP has adopted a revised guideline on clinical studies for medicines that target Alzheimer's disease. This document aims to provide guidance for the development of medicines across all stages of Alzheimer's disease.

Alzheimer's disease, a condition that destroys brain cells and nerves, disrupting the transmitters which carry messages in the brain, is the most common cause of dementia in the elderly. According to the World Health Organization

(WHO), 35.6 million people have dementia worldwide and this number is expected to double by 2030. It affects more than 5 million people in the EU.

Recent progress in understanding the pathophysiology of Alzheimer's disease suggests that the biological changes associated with the disease start to occur as early as 10 to 20 years before clinical symptoms start to appear. Many of the experimental medicines are therefore investigated in earlier disease stages as certain treatments may be more effective at that stage than later in the illness.

Currently available medicines for Alzheimer's disease only treat its symptoms. However, a number of therapies under development are targeting the biological mechanism of the condition to try and modify the course of the disease.

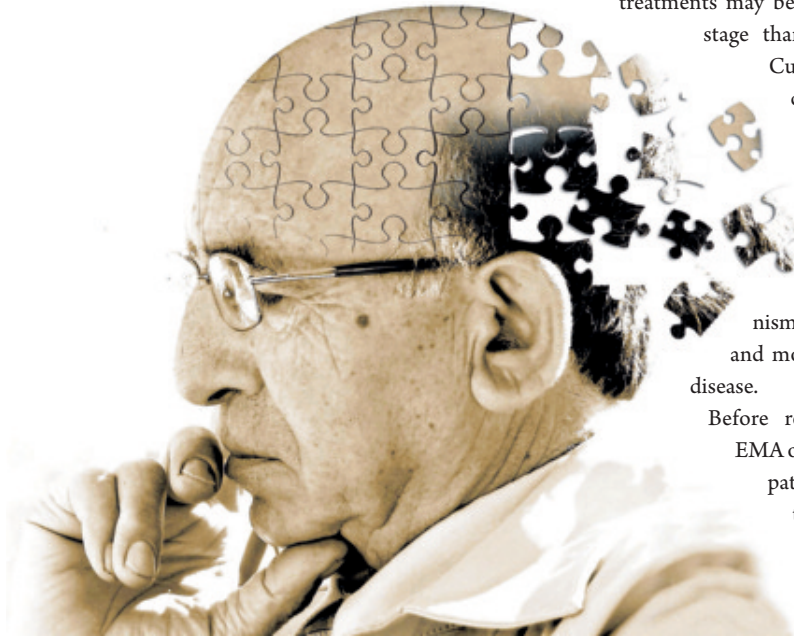
Before revising the guideline, EMA organised a workshop for patients, academia, regulators, representatives from the pharma-

ceutical industry and independent experts to ensure that it was informed of the most up-to-date scientific developments in understanding and treating Alzheimer's disease. This effort was complemented by a series of meetings between EMA and developers of medicines intended to slow down the disease progression, to discuss the issues encountered in their clinical trials. The guideline also builds on scientific advice provided by the Agency to medicine developers on specific products and methodologies, such as the qualification of biomarkers for use in clinical trials and a longitudinal model describing changes in cognition in patients with mild or moderate Alzheimer's disease.

EMA's new guideline addresses, among others:

- impact of new diagnostic criteria for Alzheimer's disease, including early and even asymptomatic disease stages, on clinical trial design.
- factors to be considered when selecting parameters to measure trial outcomes at the different disease stages in Alzheimer's.
- potential use of biomarkers in the various stages of medicine development.
- design and analysis of efficacy and safety studies.

The guideline will become effective from September 1, 2018.



## New tracking tool for EMA's relocation to Amsterdam

**March 6, 2018** – The EMA has published a new tool showing the main milestones and deliverables for the Agency's move to Amsterdam. Because of its important role to safeguard public and animal health in the EU, EMA is committed to giving stakeholders and the public full visibility of the relocation project. The tracking tool will allow all interested parties to follow the progress made.

EMA will move from London to Amsterdam before March 29, 2019, when the United Kingdom withdraws from the EU. The Dutch authorities have committed to building completely new, tailor-made premises for EMA in the Zuidas business district which are expected to be available from November 15, 2019. For an interim period until the new building is complete, EMA will occupy temporary premises in the Sloterdijk area of Amsterdam. The success of EMA's relocation is

dependent on a number of activities which need to take place in the context of these two consecutive moves.

Following the EU27 decision to relocate EMA to Amsterdam, a joint governance structure was agreed between EMA and the Netherlands with five work streams relating to the temporary and permanent premises, staff relocation, financial and legal aspects, and external communication.

The tracking tool first gives a general overview of the main milestones agreed for each of the work streams, with the exception of external communication, which is an ad-hoc activity dependent on the progress made with the other work streams. It then outlines in more detail the deliverables for each work stream, highlighting clearly if these are on track. The tracking tool is an interactive, living document that will be updated every month.





## EMA recommends immediate suspension and recall of multiple sclerosis medicine Zinbryta

**March 7, 2018** – The EMA has recommended the immediate suspension and recall of the multiple sclerosis medicine Zinbryta (daclizumab beta) following 12 reports of serious inflammatory brain disorders worldwide, including encephalitis and meningo-encephalitis. Three of the cases were fatal. A preliminary review of the available evidence indicated that immune reactions observed in the reported cases may be linked to the use of Zinbryta.

To protect patients' health, EMA is recommending the immediate suspension of the medicine's marketing authorisation in the EU and a recall of batches from pharmacies and hospitals. Healthcare professionals should immediately contact patients currently being treated with Zinbryta and should stop their treatment and consider alternatives. Patients stopping treatment must be followed up for at least 6 months.

Zinbryta was authorised in 2016 for treating relapsing forms of multiple sclerosis. Following a 2017 review of the medicine's effects on the liver, the use of the medicine was restricted to



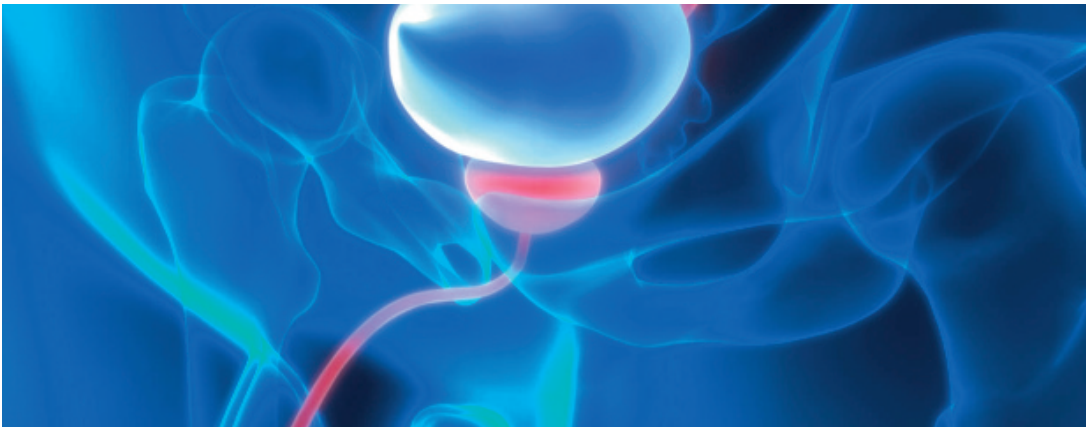
patients who have tried at least two other disease-modifying treatments and cannot be treated with any other multiple sclerosis treatments. To date over 8,000 patients have been treated with Zinbryta worldwide. The majority of EU patients have been treated in Germany.

To date EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed 12 cases of immune-mediated inflammatory disorders, including encephalitis. Most cases occurred within 8 months of starting treatment. A previous PRAC review in 2017 found that unpredictable and potentially fatal immune-mediated liver injury can occur with Zinbryta for up to 6 months after stopping treatment and concluded that patients stopping treatment should be followed up. Available evidence also

indicates that Zinbryta could be linked to other immune-mediated disorders, such as blood dyscrasias, thyroiditis or glomerulonephritis.

The review of Zinbryta was initiated following a request from the European Commission on February 26, 2018, under Article 20 of Regulation (EC) No 726/2004. EMA's recommendation to suspend Zinbryta and recall the product is being sent to the European Commission for a legally binding decision. The company that markets Zinbryta (Biogen Idec Ltd) has already voluntarily requested a withdrawal of the medicine's marketing authorisation and informed EMA of its intention to stop clinical studies. The initial review is being carried out by the PRAC, which will make a set of recommendations.

## Prostate cancer medicine Xofigo must not be used with Zytiga and prednisone/prednisolone



**March 9, 2018** – The EMA has recommended contraindicating the use of the prostate cancer medicine Xofigo (radium-223 dichloride) with Zytiga (abiraterone acetate) and prednisone/prednisolone, due to an increased risk of death and fractures with this combination.

EMA's PRAC has reviewed the preliminary data from an ongoing clinical study in metastatic prostate cancer patients. In this study 34.7% of patients treated with Xofigo, Zytiga and

prednisone/prednisolone have died so far, compared with 28.2% of patients given placebo, Zytiga and prednisone/prednisolone. Fractures have also occurred more frequently with the Xofigo combination than the placebo combination (26% versus 8.1%).

Xofigo is currently authorised for use in men whose prostate cancer has spread to the bones and is causing symptoms. The ongoing clinical study includes metastatic prostate cancer patients

who have not previously received chemotherapy and who have no symptoms or only mild symptoms, such as pain. Patients have completed the Xofigo part of the study, and the combination is no longer being used; all the patients involved are being monitored closely.

Healthcare professionals in the EU must not use a combination of Xofigo with the anti-androgen Zytiga and prednisone/prednisolone, and should stop this combination in

men currently treated with it and review the treatment for these patients. Healthcare professionals are also warned that the safety and efficacy of Xofigo in combination with a class of medicines called second generation androgen receptor antagonists, such as Xtandi (enzalutamide), have not been established.

These are temporary measures until the ongoing in-depth review of the benefits and risks of Xofigo is complete.



## Winners of the Geoff Hall Scholarship Essay Competition

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 on the basis of an essay competition, and the title of this year's essay was "Creative Medical Writing: An Oxymoron?". There were even more entries than last year, and it was not an easy task to choose just two winning entries. However, two were eventually chosen, and the very worthy winners were Marisa Granados and Amy Joughin Parr.

Marisa Granados' interest in science led her to obtain two degrees in biotechnology, researching the production of biopharmaceuticals and stem cell growth. Marisa completed her PhD in Regenerative Sciences at Hanover Medical School in 2016, working on the development of scaffolds

### FOR CORRESPONDENCE



**Lisa Chamberlain James**

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for the replacement and repair of the mitral valve by using decellularised tissue. Following her PhD, she moved to Gdansk, Poland, with her husband. Although she found her research interesting, she realised that what she enjoyed most was communicating it. Thus, after years of doing bench work she decided to move away from the lab and pursue her love of writing. Marisa was drawn to medical writing because of its broad scope. She enjoys the challenge of transforming complex research findings into different types of publications. In her free time Marisa loves reading and writing fiction, spending time in nature, and scuba diving.

Amy Joughin Parr qualified as a dentist in 2004 and has worked in general practice ever since. She is interested in evidence-based

dentistry, and received a research fellowship from the National Institute of Health Research in 2008 that allowed her to undertake research into chronic facial pain at the University of Manchester whilst continuing to work in practice. Amy has a master's degree in public health, an undergraduate degree in psychology and philosophy, a postgraduate diploma in healthcare law and ethics, and postgraduate qualifications in endodontology and restorative dentistry. She loves to read and write and hopes to find a part-time medical writing internship in the near future.

Marisa's and Amy's winning essays are presented in this section, and we wish them the very best at the start of their very promising medical writing careers. For those of you inspired by their achievements, this year's essay title is "The medical writer: Partner or servant?" The submission deadline is September 30, 2018.

I hope to read your essays soon!

**Bestest,  
Lisa**

# Creative medical writing: An oxymoron?

According to the *Merriam-Webster Dictionary*, creativity is “the ability to create”, and to create means “to make or bring into existence something new.”<sup>1</sup> As it applies to writing, creativity is most often associated with imaginative, fictional accounts. Yet, creative nonfiction is a well-accepted literary genre, suggesting that a text can be both factual and creative. In this essay, I contend not only that medical writing can be creative, but that it should be.

Medical writing is about clearly communicating medical information. The message needs to be clear, complete, factual, and accurate. However, effective communication entails more than simply gathering and relaying information. If the writer were to present only the dry results of scientific research, the text would quickly become tiresome. Instead, for communication to be successful, it must engage the reader’s attention, and this requires creativity. In fact, studies show that communicating scientific findings using storytelling, rather than dry, numerical results, improves the readers’ attention and makes the information easier to process and remember.<sup>2</sup> This is particularly important in the context of medical writing, where the messages being communicated can have an important effect on the health of people.

Engaging, and keeping, the attention of the reader means the writer has to simplify the information being communicated. Results from scientific and medical research are complex and are often difficult to understand for the non-specialised reader. The medical writer not only needs to translate jargon, but also to explain the scientific findings in a way that conveys meaning to his particular audience. For example, numbers are an important component of medical research results, and yet studies show that many people lack the appropriate numeracy skills to understand and interpret these results.<sup>2</sup> Research in the area of health care has shown that patients are more likely to understand the information and make correct choices when it requires less effort on their part to understand it.<sup>3,4</sup>

Moreover, results from scientific research must often be considered in the context of other research findings or in light of what others have done. In her essay “What Medical Writing Means To Me,” Elizabeth Wager wrote, “It is a fallacy to believe that science can be reported completely dispassionately and without some form of interpretation.”<sup>5</sup> Readers can easily become lost

in the wealth of information resulting from medical research. It is the task of the writer to point the reader to the most relevant results and to show the significance of those findings. Simplifying and interpreting the data, and adjusting the message to a particular audience entails creativity.

Thus far, it seems that creativity is indispensable in the broad field of medical communications. However, even in regulatory writing, where the writer is more tightly constrained by the need to conform to strict guidelines, creativity is still essential. This is because medical writers working on regulatory documents need to read and analyse a range of reports and then condense and synthesise the information for the readers. It is not just about simplifying jargon and reducing the complexity inherent to scientific results, but about combining different sources and finding connections between ideas to create something new.

Like gymnasts performing on the balance beam, medical writers dance on the narrow boundary between scientific accuracy and expressiveness. The purpose of medical writing is, above all, to communicate, and effective communication requires creativity. The medical writer needs to craft a tailored message that is not only factual and accurate, but also accessible. Precision and simplification must be balanced to reach a level that is “just right”, neither unnecessarily complicated nor vague. As the 20th century American jazz player and composer Charles Mingus said, “Making the simple complicated is commonplace; making the complicated simple, awesomely simple, that’s creativity.”<sup>6</sup>

**Like gymnasts performing on the balance beam, medical writers dance on the narrow boundary between scientific accuracy and expressiveness.**



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# Creative medical writing: An oxymoron?

Is “creative medical writing” an oxymoron? I sincerely hope not! Indeed, if this is the case I will be sorely disappointed, as it is a career I wish to pursue precisely because it may allow me to exercise some creativity. I enjoyed both the arts and the sciences at school, and finding a career that involved both proved difficult. Indeed, teachers advised that I choose one or the other to avoid looking noncommittal in future university applications. I chose science, and I don’t regret that. I then chose a job that would allow me to exercise some artistic flair, dentistry.

However, there is a limit to exactly how much creativity one can bring to the surgery as an “ivory carpenter”. Whilst my patients are grateful to have their teeth carefully restored to their original appearance, they would not be pleased to leave my surgery with a rendering of the Mona Lisa carved into their incisor. Nor will my copious, painstakingly accurate notes be a likely contender for the Pulitzer Prize.

Whilst exploring career options within dentistry, I was lucky enough to win a fellowship to undertake research training and soon discovered that it wasn’t the research I enjoyed so much as the writing. However, funding in dental research does require that you do some actual research to write about, so I returned to my surgery to mull over other possibilities.

After some Internet research I happened upon a job description I hadn’t been aware of, for “medical writing”. The more I read about it, the more excited I became. It seemed the perfect marriage of my love for science and writing, and I have been considering this career move ever since. Unfortunately, day to day life has a way of taking over, and I hesitated to take the first step. Since the birth of my son, however, I realised that if he was in my situation, I would encourage him to pursue a career that he would enjoy. So would I enjoy it? Is it a creative occupation? Which brings us neatly to the question, “Is creative medical writing an oxymoron?”

In order to decide, it would be helpful to look at the meaning of an oxymoron. “Oxy” comes from the Greek word *oxus*, meaning “sharp”. The meaning of “moron” may be more easily deduced, sharing its etymological origins with antiquated psychological terminology. “Moron” is also from Greek, *moros*, meaning stupid. An oxymoron is essentially where contradictory terms are used in conjunction as a rhetorical device. The word oxymoron is autological; the word oxymoron is



itself an oxymoron.

So are “creative” and “medical writing” contradictory terms? Let us define the terms first. Medical writing has been described as “writing scientific documents of different types, which include regulatory and research-related documents, disease or drug-related educational and promotional literature, publication articles like journal manuscripts and abstracts, content for healthcare websites, health-related magazines or news articles”.<sup>1</sup> Broadly speaking these documents fall into one of two categories: regulatory writing, and medical communications, often abbreviated as MedComms.

With regard to the definition of “creative”, the *Oxford English Dictionary* defines it as “adj. 1. inventive, imaginative. 2 able to create”. The *Collins English Dictionary* defines “creative writing” as “writing which is imaginative and inspiring, esp fiction”.

Medical regulatory documents follow a structured format with specific requirements, often involving the synthesis of large amounts of data restructured in a clear and concise manner. It seems unlikely that such work would provide much scope for “writing which is imaginative and inspiring”. Furthermore, in the world of accounting, being “creative with the figures” is often used as a euphemism for presenting data in a misleading manner. If the same “creativity” were applied to regulatory writing, those providing the original data would likely not be appreciative. Such an approach is unethical and could lead to serious consequences. Therefore with regard to medical regulatory writing it could be argued that “creative medical writing” is indeed an oxymoron.

On the other hand, one could contend that you are being creative in regulatory writing in that you are creating something new. Certainly it

would be considered plagiarism to simply copy and paste sections of text and data. However, such an argument does seem to be pushing the definition of creativity to its limits. A stronger case for creativity in medical writing could be made for medical communications.

As described previously, medical communications involves a wide range of writing, and the potential audience and purpose for such writing is equally wide. Unlike regulatory writing where the target audience is obliged to read the documents, with medical communications one may need to entice and persuade the reader. Here creativity in terms of “writing which is imaginative and inspiring” may well be a useful asset. Arguably some work, such as writing research articles, has less scope for creativity than others, but even here one needs to hold the attention of the reader and ensure the experiment, data, and conclusions are presented in a clear and compelling manner.

In conclusion, is “creative medical writing” an oxymoron? I would argue that although medical writers cannot be creative with the facts and data that form the basis of their communications, in areas such as medical marketing, education, and journalism they have a wide scope to be creative in order to get their messages across to their intended audience. So no, thankfully for my future career aspirations, creative medical writing is not an oxymoron!

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# Profile

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## An interview with Chris Winchester

Chief Executive Officer of HealthScience communications consultancy  
Oxford PharmaGenesis and a leading member of Open Pharma

*Put on your hiking boots and take a ramble through the bucolic countryside of Oxfordshire. As you roam amongst the winding tributaries of the Thames, meandering between verdant rolling hills and quaint village pubs, you may come across Tubney Warren Barn. At first glance, it looks just like any other farm building, standing serenely amidst the chatter of birdsong and the nearby sounds of a village cricket match. However, beneath its rustic exterior, the building is a hive of activity. This is the office where Oxford PharmaGenesis was born, and from which it has gone on to become one of the largest independent players in its field, with over 200 employees in seven offices around the world. We've come here to meet the company's CEO, a man who is also one of the driving forces behind Open Pharma, Chris Winchester.*

**MEW:** Hi Chris, thanks for agreeing to talk to us. First, tell us a bit about Oxford PharmaGenesis – how did the company start out, how did you get involved, and how did you come to be based in a barn?

**(CW):** Oxford PharmaGenesis was founded in 1998 by Dr Graham Shelton who, after lecturing in Zoology at Oxford, moved into publishing and communications. With his new company, he set out to create an environment in which talented people could deliver excellent quality to clients they liked. Our premises have always been an important part of that environment, and we were lucky enough that Graham found and renovated an eighteenth-century listed barn in a lovely location just outside Oxford. I joined the company 15 years ago, by which time that barn was home to 14 of us, and we have now expanded into two more buildings on the same site, as well as premises in central Oxford, London, Cardiff, Basel, and Philadelphia, with a new office opening in Melbourne, Australia. We recently marked



**Chris  
Winchester**

our 20th anniversary at St Catherine's College, Oxford, at which we celebrated our independence under the rallying cry "our future, our values".

**MEW:** Congratulations and happy birthday! What would you say are the key factors in

remaining successful – and independent – for such a long period of time?

**(CW):** Our independence is central to our success, as it allows us to take a long view, prioritising our values of high-quality delivery and client service coupled with a commitment to social responsibility. These enable us to build

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lasting relationships with clients, colleagues, patients, and experts in their field. We pride ourselves on having a highly engaged workforce, with 86% of employees saying that we are a great place to work, and an employee turnover of below 10%. In 2012, a group of employees worked with Graham to secure the independence of the company through a management buy-out, and Graham remains our Chairman to this day. The fact that all our shareholders are actively engaged in our business enables us to deliver our strategy of staying close to our clients and supporting them as they move into exciting new areas.

**MEW:** Tell us a bit about your personal story: What drove you to work in this field, and what would you say are the main changes that have happened in our industry during this time?

**(CW):** I was attracted to biochemistry because of a curiosity about how organisms work in health and disease. However, my practical partners and supervisors can attest that, despite my best

efforts, I was not a natural in the lab. My doctoral supervisor said that he thought I could write, so when I hung up my lab coat I looked for jobs in science communication. After a brief stint as a management consultant, I got stuck into medical communications and haven't looked back. What really appeals is being able to use my scientific training to make a difference to patients' lives.

The biggest change I have seen in my 17 years in the industry is the recognition of publications as a discipline with its own specialist skills. Since 2001, we have seen the launch of Good Publication Practice (GPP) guidelines, the first position statements on the role of the professional medical writer, publication departments set up and moved into medical affairs, and the birth of the International Society for Medical Publication Professionals (ISMPP), which I currently chair. Professional organisations such as EMWA, AMWA and ISMPP play an important role in sharing best practice in our industry, and I was delighted to be invited by EMWA to co-lead the development of the first global

standard for professional medical writers, the AMWA–EMWA–ISMPP Joint Position Statement, which was launched last year.<sup>1</sup>

**MEW:** The theme of this issue is "Public Disclosure". Why do you think this is important, and what impact do you think that timely public disclosure of clinical research could have on public health?

**(CW):** Our clients in the research-based pharmaceutical industry work incredibly hard to generate evidence characterising the safety and effectiveness of their medicines. The end users of evidence generated by the pharmaceutical industry need to be confident that they have all the information they need to make informed decisions. Only with complete disclosure will doctors, patients, payers, and others have the confidence to use new medicines to improve human health.

**MEW:** You're one of the driving forces behind Open Pharma. Tell us a bit about what this project is, and how it started.

**(CW):** Open Pharma was sparked by a discussion with a client one evening after the launch of the GPP3 guidelines. We went from discussing the flaws in the current model for publishing industry-funded biomedical research to wondering what we could do about it. After talking to a wide range of other stakeholders, we realised that there was broad recognition of the need for change, but that the pharmaceutical industry was largely left out of discussions about potential solutions.

We have brought together a group of forward-thinking pharmaceutical companies, publishers, patients, academics, regulators, editors, non-pharmaceutical funders, and societies to understand the role that the pharmaceutical industry could play in improving the publication of biomedical research. In particular, we have been excited to learn about specific initiatives in other sectors that may be applicable to our industry, including mandatory open-access policies, author identifiers such as ORCID, and preprints.

**MEW:** How do you think the pharmaceutical industry compares with academia in terms of publishing the results of its research?

**(CW):** Industry critics may be surprised to learn that the pharmaceutical industry is actually better at disclosing the results of clinical trials than most other groups, including academic, governmental, and charitable research funders. Research we conducted with fellow EMWA member Slavka Baronikova and colleagues showed that nearly



*Tubney Warren Barn, Oxfordshire, England*

three quarters of industry-sponsored trials are disclosed, compared with less than half of non-industry trials.<sup>2</sup> Disclosure of trials supporting FDA- and EMA-approved drugs is even better: typically 100%. And consequently, pharmaceutical companies perform well in the recently launched Food and Drug Administration Amendments Act (FDAAA) TrialsTracker from Ben Goldacre and the Oxford Centre for Evidence-Based Medicine, which measures compliance with the American FDAAA legislation.<sup>3</sup>

**MEW:** Why do you think this is?

**(CW):** Industry is used to working in a highly regulated environment, and meets its legal and ethical commitments by deploying appropriate internal and external resources, including professional medical writers and project managers in communications companies such as our own. Following in the footsteps of EMWA member Adam Jacobs, we at Oxford Pharma-Genesis have undertaken collaborative research demonstrating how we help the authors of industry-funded research to publish in an ethical, accurate, and timely manner.<sup>4-7</sup>

**MEW:** What message would you give to our readers, many of whom are dealing with the issue of publishing clinical data on a day-to-day basis? How can we have an impact?

**(CW):** Keep at it! We are likely to see big changes in the publishing of research from the pharmaceutical industry, which have the potential to strip away non-value-added activities involved in submission, resubmission, and author disclosures. What will be left is the core of high-quality, evidence-based communication. We can feel genuinely proud of the value we add to evidence-based medicine, and we must not be shy of sharing our own evidence of benefit with the people we work with every day. Just as

importantly, why not consider conducting your own research into the value of professional medical writing support? There is no better way to face the future than by being able to demonstrate that we do an outstanding job.

**MEW:** A lot of our readers are new to the field of medical communications. Based on what you've learned in your time, what advice would you give to someone starting out in the industry today?

**(CW):** Our industry crosses many disciplines, and is demanding and rewarding in equal measure. Cold, hard data are central to what we do, but ultimately human relationships are key. Therefore, it is important to be as open and honest as possible, no matter how difficult things get, because by gaining a reputation for integrity, and by getting the detail right, you can build the enduring, trusting relationships that will take you places, both literally and metaphorically.

**MEW:** And finally, when you're not championing open science or managing a successful company, what do you get up to in your spare time?

**(CW):** I enjoy playing the double bass in my local orchestra, spending time with my family, and pottering in the garden.

**MEW:** And finally, some quick-fire questions:

**Beach break or skiing holiday?**

Skiing holiday

**Brahms or Beatles?**

Brahms

**Getting around Oxford: cycling or punting?**

Cycling

**Classic novel or non-fiction?**

Classic novel if time – otherwise non-fiction, preferably a good biography

**Football or rugby? (or neither!)**

Neither!

**Pen and paper or word processor?**

Pen and paper by choice, word processor by necessity

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## Contact information

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# Journal Watch

Journal Watch is based on the French-language blog *Rédaction Médicale et Scientifique* by Hervé Maisonneuve available at [www.redactionmedicale.fr](http://www.redactionmedicale.fr).

## SECTION EDITOR



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## Good Practice for Conference Abstracts and Presentations: GP-CAP

Guidance for conference abstracts and presentations of company-sponsored research is not uniform. Each conference has its recommendations, and there is a need for consistency. A group of editors and communicators has posted a preprint describing the GP-CAP (Good Practice for Conference Abstracts and Presentations). The authors are gathering comments on the draft guidelines, with a plan to revise and publish the document. There are recommendations for researchers and for conference organizers.

1. Authorship: authors (see International Committee of Medical Journal Editors [ICMJE] and GPP3), contributors/study groups, and presenters/ society sponsors are described. Listing fewer than 10 authors and study group names is recommended. "In certain circumstances, and if all authors agree, it is permissible for somebody whose contribution does not (or will not) meet the ICMJE authorship criteria for a journal article to present findings at a conference."
2. Conference abstracts: These should include a study identifier such as a registration number (for clinical trials), study name,



protocol number, or grant number. "Most conferences will not consider reports of findings that have already been published in full (i.e., in a peer-reviewed journal). This requirement must be respected and, even if permitted, presenting findings after full publication should be avoided."

3. Encore abstracts: "It is permissible to present the same research findings at more than one conference if both the first and subsequent conferences allow this. This practice may be referred to as an *encore* (or, more specifically an *encore abstract* or *encore presentation*). However, presentations of the same findings to the same audience should be avoided."
4. Conference presentations (slides and posters): "Author listing and sequence on posters and oral presentations should be the same as that on the abstract. Authors should

not be added to a presentation after the abstract is accepted.... If research findings change substantially between abstract submission and conference presentation and this change affects the conclusions of the research, we recommend that authors alert the conference to this discrepancy... Posters are not peer-reviewed by conferences and may not describe all aspects of the research. Posters should therefore not be viewed as a substitute for a full article in a peer-reviewed journal."

## Reference

Foster C, Wager E, Marchington J, Patel M, Banner S, Kennard NC, et al. Good practice for conference abstracts & presentations: GP-CAP. Peer J Preprints. <https://peerj.com/preprints/3356/>

## Catalogue of bias

The Center of Evidence-Based Medicine (CEBM), University of Oxford, has launched a Catalogue of Bias, an online resource at <https://catalogofbias.org/biases> that features definitions of the types of bias that can affect health research. The worthwhile effort is supported by the McCall MacBain Foundation. Currently, there are 30 entries with a short definition. The team wants to expand the list and they welcome any suggestions or comments.



## Transparency in authors' contributions and responsibilities

A preprint posted on bioRxiv then later published by *Proceedings of the National Academy of Sciences* is a position paper about author contributions and responsibilities signed by 13 editors from prestigious bio-medicine journals.<sup>1</sup> They adapted the ICMJE criteria for authorship and recommended that journals adopt the following statement as a best practice for crediting all authors of a paper:

*Each author is expected to have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND to have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.*

Other recommendations are:

- Roles for the corresponding authors: “ensuring that all listed authors have approved the manuscript before submission and that all authors receive the submission and all

*substantive correspondence with editors, as well as the full reviews, verifying that all data, materials (including reagents), and code, even those developed or provided by other authors, comply with the transparency and reproducibility standards of both the field and journal;”*

- “To discourage ghost authorship, corresponding authors must reveal as appropriate whether the manuscript benefited from the use of editorial services that, if unacknowledged, might constitute an undisclosed conflict of interest.”
- Journals should use the 14 CRediT taxonomy categories for contributor roles; CRediT stands for Contributors Roles Taxonomy;<sup>2</sup>
- All journals in the physical, life, and social sciences should require that authors have an ORCID iD;
- Universities/research institutions, funding agencies, and scientific societies should strongly endorse efforts to increase transparency.

The French national institute of health and



medical research (Inserm) has issued a nice brochure on authorship good practices.<sup>3</sup> They have internal data showing that 40% of the individual files ( $n = 100$ ) processed over 10 years by the scientific integrity office related to conflicts concerning the list of authors. The list of co-authors is a sensitive subject, as researchers are assessed on publications. The topics are: What are the ethical rules to be applied? How can authorship be determined? The document also provide advice for how to address these issues throughout the duration of a project and editorial submission.

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## RCTs published in *The BMJ* and *PLOS Medicine* can be reanalysed when authors share data



Naudet and colleagues undertook a large project to determine the effectiveness of data sharing policies in *The BMJ* and *PLOS Medicine*. The researchers gathered data from 37 published

randomised controlled trials (RCTs) and reanalysed primary outcomes. In reassuring findings, the reanalyses mostly yielded similar results. Methods are detailed in the paper and all data are available. It showed that the sharing data policy, as recommended by ICMJE, can be implemented, even if not optimal.

The study notes the following:

- *Data availability was not optimal in two journals with a strong policy for data sharing, but the 46% data sharing rate observed was higher than elsewhere in the biomedical literature.*
- *When reanalyses are possible, these mostly yield results similar to the original analysis; however, these reanalyses used data at a mature analytical stage.*
- *Problems in contacting corresponding authors,*

*lack of resources in preparing the datasets, and heterogeneity in data sharing practices are barriers to overcome.*

Few journals have a strong data sharing policy, so the potential to reanalyse data from RCTs published in specialty journals is questionable. We need further similar research studies to improve our confidence in publications.

### Reference

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## Inconsistent reporting between protocols or registrations and full reports of primary biomedical research

Researchers from McMaster University, Hamilton, Canada, searched databases to survey the existing evidence of inconsistencies between protocols or registrations and full reports published in biomedical journals. They searched studies in English up to September 30, 2016. They followed guidance to perform a systematic review, retrieved 9123 records, and included 37 studies (33 surveys and 4 systematic reviews) for analysis. They observed high levels of inconsistency between the described research plan in protocols/registrations and what was reported in the journal literature for the categories of outcome reporting (ranging from 14% to 100%), subgroup reporting (from 12% to 100%), statistical analysis (from 9% to 47%), and other measure comparisons. Some factors, such as outcomes with significant results, sponsorship, type of outcome, and disease specialty were reported to be significantly related to inconsistency reporting.

This 20-page article contains many troublesome examples from RCTs (complete references are in the paper):

- 49% (75/152) showed some discrepancies in outcomes, most related to introducing or omitting a primary outcome; 28% (21/75) of these discrepancies favored statistically significant results;
- 29% (32/108) of registered trials had a



discrepancy of primary outcomes between registrations and full reports; 92% of the discrepancies in primary outcomes (in 22 out of 24 full reports) favored a statistically significant finding;

- 100% (69/69) of full reports had discrepancies in primary outcome specifications (POS); 30% (21/69) of full reports had unambiguous POS discrepancies, with significantly higher percentages of non-industry-sponsored than industry-sponsored full reports having unambiguous POS discrepancies;
- 19% (17/88) of full reports were registered;

45% (32/71) of full reports had inconsistency of primary outcomes; 71% (15/21) had discrepancies in primary outcomes that favored significant findings.

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Li G, Abbade LFP, Nwosu I, Jin Y, Leenus A, Maaz M, et al. A systematic review of comparisons between protocols or registrations and full reports in primary biomedical research. *BMC Medical Research Methodology*. 2018;18:9. <https://doi.org/10.1186/s12874-017-0465-7>.

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# In the Bookstores

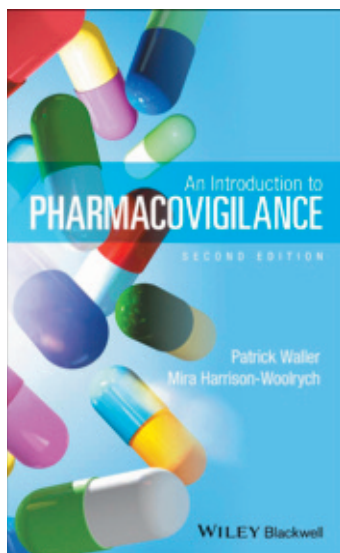
## An Introduction to Pharmacovigilance (Second Edition)

By Patrick Waller and Mira Harrison-Woolrych  
Wiley-Blackwell  
ISBN: 978-1-119-28974-6  
£29.99; 192 pages

*An Introduction to Pharmacovigilance* is a compelling read and one that both new and experienced medical writers will find useful for providing a succinct, yet thorough, overview of today's current drug safety requirements. Patrick Waller and Mira Harrison-Woolrych are experts in pharmacovigilance; their wealth of knowledge makes this second edition book a must have on any medical writer's desk and provides a more up-to-date and internationally focused work than its predecessor.

The book is organised into 10 chapters and these are ordered into several topics such as the processes and societal considerations of pharmacovigilance, making it easier to find specific areas of interest to the readers. To open the medical writer's eyes to the importance of drug regulation, Chapter 1 starts at the beginning of modern pharmacovigilance, with thalidomide, and how the terrible consequences of poor safety monitoring led to legislation that was the forebear of what is in place today. From here the authors go on to discuss other more recent drug scandals, from practolol in the 1970s up to pandemrix in 2009, to give a wide-ranging timeline of pharmacovigilance evolution that brings further clarification to how vital drug safety regulations have been put in place to protect patients taking drugs.

Chapter 2 segues into an outline of basic concepts, from adverse drug reactions (ADRs) and their systems of classification to the risk-benefit balance and how to evaluate causality. Chapter 3 offers summaries of the multiple clinical trial phases, followed by safety reporting methods (for example, spontaneous ADR reporting systems and prescription-event monitoring) that are employed by different agencies to further build the profile of a drug once marketed. The overall process of pharma-



covigilance is then followed up within Chapter 4, where the authors explain ADR signal detection techniques and their merits, signal evaluation and prioritisation, and the different courses of action that can be implemented. The assumption that all readers would be aware of the statistical methods mentioned in this chapter, such as Bayesian statistics, is a potential weakness, and I personally would have found it beneficial to go into these methods in

more depth. However, the overarching messages of this chapter are the importance of communication in pharmacovigilance and the need to assess the adequacy of actions once completed, which are both conveyed excellently.

Chapter 5 reviews how pharmacovigilance procedures are regulated, starting with a focus on the authors' own line of expertise – drug safety within the EU. We are presented with many of the EU's rules and objectives regarding pharmacovigilance, such as the need to increase efficiency and transparency with regard to drug safety to ensure patient welfare whilst on medication. Additional guidelines such as the European Medicines Agency's 12 modules on Good Pharmacovigilance Practices

and guidelines on the Summary of Product Characteristics are introduced and described alongside the obligations imposed upon pharmaceutical companies to guarantee that the products they sell and research are fully compliant. The subsections on periodic safety update reports and risk management planning might be of particular interest to medical writers, due to the likelihood of having already worked on these documents or needing to in the future.

In Chapter 6, the authors

We are presented with many of the EU's rules and objectives regarding pharmacovigilance, such as the need to increase efficiency and transparency with regard to drug safety to ensure patient welfare whilst on medication.

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continue the theme of pharmacovigilance regulation by reviewing the international coordination that takes place to ensure drug safety is monitored appropriately and that relevant safety information is shared between parties immediately to prevent further worldwide issues. They focus mainly on the larger regulatory bodies relevant to safety, such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Council for International Organizations of Medical Sciences (CIOMS), and also highlight the role of other types of organisations, including international professional societies, such as the Drug Information Association (DIA). This offers the reader a greater understanding of the huge efforts the healthcare community employs to ensure pharmacovigilance information is collated and shared to reduce patient risks. Chapter 7 then delivers an overview of how pharmacovigilance affects patients on a day-to-day basis, exploring the consequences of ADRs for patients within all walks of life and outlining important ADRs such as gastrointestinal bleeding and agranulocytosis. The rest of the chapter then assesses how work in the clinic can help to limit ADR occurrence.

Tasks mentioned include checking up routinely on the well-being of patients who are taking new medication and taking additional care when prescribing to specific patient populations such as the elderly, who are more at risk of ADRs than other populations.

Chapter 8 dissects the ethics of pharmacovigilance, looking specifically at common ethical principles within the pharmaceutical industry (informed consent, privacy/confidentiality), and examining the safeguards that are put in place, such as ethics committees/review boards. The penultimate chapter of *An*

*Introduction to Pharmacovigilance* then discusses how pharmacovigilance is expected to evolve, by judging its current limitations and what can and is being done to overcome them. The final chapter recommends where to go next for those interested in learning more by providing a range of books and journals for suggested reading, as well as courses that can be attended and relevant societies that the reader could join.

Overall this book is an interesting read that provides a wealth of knowledge on numerous aspects of pharmacovigilance. As a medical writer with 2 years' experience, I did already have an understanding of some sections, but this book expanded on my awareness and understanding of

pharmacovigilance, and it delivered a much broader education on current pharmacovigilance concerns. In particular, I thought the introduction was very effective in stressing the role of pharmacovigilance in healthcare, by examining several drug scandals and determining how each of these in turn has shaped pharmacovigilance. Other chapters, such as those concerning ethics and pharmacovigilance in the clinic, put pharmacovigilance into perspective with regard to everyday living, and these chapters were, in my opinion, especially successful at complementing some of the more information-heavy chapters explaining procedure. Although some of these information-heavy chapters might

be a bit of a hard read in one go, they are extremely informative and are a brilliant companion to have with you at your desk when working on a pharmacovigilance project. In general, this is a very useful book that could improve any medical writer's understanding of the state of pharmacovigilance today.

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Save the date:  
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**WARSAW**  
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# Good Writing Practice

## Paragraph order distraction

Backtracking: pronoun, synonym



### Introduction

Backtracking distracts paragraph order by inducing re-reading previous text. Such backtracking is a more serious distraction when it occurs between sentences than within sentences, because the distance between a referent (pronoun or synonym) and its antecedent is longer inter-sentence than intra-sentence.

### Pronoun-induced backtracking

The neutral personal pronoun (*it*), the indefinite pronoun (*both* and *others*), and demonstrative pronouns (*this*, *that*) – all of which are inherently implicit and common in research writing – necessitate referring back to an antecedent (i.e., a noun or previous textual information).

### Part 1 – Personal pronoun-induced backtracking

**Example: Introduction section, hypothesis justification**

*As described in case reports, root coverage is extensive by the Vestibular Incisor Subperiosteal Access (VISTA) technique. Furthermore, it provides evident biological advantages.*

### Revision (antecedent abbreviation)

*As described in case reports, root coverage is extensive by the Vestibular Incisor Subperiosteal Access (VISTA) technique. Furthermore, VISTA provides evident biological advantages.*

### Notes

The antecedent for *it* could be root coverage or it could be the VISTA technique. Using the antecedent abbreviation VISTA clarifies the antecedent whilst avoiding repetition of *Vestibular Incisor Subperiosteal Access*.

### Part 2 – Indefinite pronoun-induced backtracking

**Example: Introduction section, objective + experimental approach**

*Therefore, this relation can be modelled in a robust fashion and presented to clarify the strength of the relation and to resolve residual uncertainties about the relation. Bayesian hierarchical modelling is suitable for both purposes.*

### Revision 1 (appositive restatement)

*Therefore, this relation can be modelled in a robust fashion and presented to clarify the*

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*strength of the relation and to resolve residual uncertainties about the relation. Bayesian hierarchical modelling is suitable for both purposes: **clarification and resolution**.*

### Revision 2 (enumerated antecedent)

*Therefore, this relation can be modelled in a robust fashion and presented (1) to clarify the strength of the relation and (2) to resolve residual uncertainties about the relation. Bayesian hierarchical modelling is suitable for **both** purposes.*

### Notes

The indefinite adjectival pronoun *both* in combination with a noun *purposes* elicits a backtracking comparable to the personal pronoun *it*. Although the antecedents to *both* are fathomable, minimising backtracking enhances immediate comprehension. In Revision 1, to avoid backtracking, the purposes (*to clarify...to resolve*) are each restated in a noun form: *clarification* and *resolution*. In Revision 2, numbering is useful to forecast and emphasise the antecedents thereby facilitating backtracking.

### Part 3 – Demonstrative pronoun-induced backtracking

**Example: Materials and Methods section, method**

*The neurologic test scores were analysed by Cluster Analysis. **That** enabled subgroup identification for the sample of girls with AIS.*

### Revision (syntactic reduction + sentence combining)

*The neurologic test scores were analysed by Cluster Analysis **to enable** subgroup identification for the sample of girls with AIS.*

## Notes

In the Revision, the second sentence beginning with *that* is transformed (syntactic reduction) + translocation (sentence combining) into an infinitive phrase, which conveys intent.

Placement of the infinitive phrase after the verb is preferred, because placement in an initial sentence position suspends the long infinitive phrase overly delaying the subject and verb of the sentence. To some readers, the infinitive phrase may be thought to dangle, that is, be devoid of a modifier, such as *a neurologist*. However, the phrase can function adverbially modifying *were analysed*. A test for this adverbial function is transposition of the phrase to after the verb, a position not plausible if the phrase were strictly adjectival. Clearly, the infinitive phrase is not modifying the noun phrase *Cluster Analysis*.

## Part 4 – Demonstrative pronoun-induced backtracking

**Example: Results section, data-based observation + preliminary interpretation**

*As shown by the superimpositions, the observed movement frequency was the most for rotation and the least for bodily movement. That was likely due to the remaining band space at debond.*

### Revision (summative concept)

*As shown by the superimpositions, the observed movement frequency was the most for rotation and the least for bodily movement. **That frequency difference** was likely due to the remaining band space at debond.*

## Notes

Replacement of *that* with *that frequency difference* eliminates any doubt about the antecedent of *that* and minimises backtracking to identify the antecedent.

*That* (not *this*) seems contextually dictated by the past tense of the predicate *was* in the first sentence.

## Synonym-induced backtracking

In research writing, the repetition of a word (usually a noun) as a synonym is often a distraction, because no two words have exactly the same meaning. Contrary to the advice that synonyms engender interest, synonym usage (i.e., synonymy) may be interesting but at the expense of continuity – synonymy is inconsistent.

Synonymy also elicits backtracking to the synonym antecedent.

## Part 1 – Patients ... participants

**Example: Materials and Methods section, method**

*Post-stroke patients (n=361) with mild to moderate upper extremity impairment were enrolled in the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE), a randomised controlled trial of arm intervention. After the trial, the patient-reported outcome (the Stroke Impact Scale) was completed by the participants.*

### Revision (expanded noun antecedent)

*Post-stroke patients (n=361) with mild to moderate upper extremity impairment were enrolled in the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE), a randomised controlled trial of arm intervention. After the trial, the patient-reported outcome (the Stroke Impact Scale) was completed by the **enrolled patients**.*

## Notes

Instead of using the synonym *participants*, clarity is achieved by repetition of the antecedent patients in an expanded form (*enrolled patients*).

## Part 2 – Disks ... samples

**Example: Materials and Methods section, materials**

*Composite disks (5.0 mm thickness × 14 mm diameter; Paradigm MZ100) were cemented to the blocks using dual-cure resin cement (RelyX Ultimate). Samples were polymerised (40 s), artificially aged (20,000 thermal cycles), sectioned (0.8 ± 0.2 mm), and tested for micro-tensile bond strength.*

### Revision (expanded antecedent)

*Composite disks (5.0 mm thickness × 14 mm diameter; Paradigm MZ100) were cemented to the blocks using dual-cure resin cement (RelyX Ultimate). **Cemented disks** were polymerised (40 s), artificially aged (20,000 thermal cycles), sectioned (0.8 ± 0.2 mm), and tested for micro-tensile bond strength.*

## Notes

Switching from *disks* to *samples* generates

uncertainty. In a sequence of effects on an entity, explicitly denoting the change in the entity to an expanded form (e.g., *disks* to *cemented disks*) facilitates clarity and tempers the monotony of repetition.

## Part 3 – Limited ... limitation

**Example: Discussion section, hypothesis-support limitation**

*However, these results may have been limited by the current CBCT resolution to accurately delineate the maxillary cancellous bone. Another shortcoming was that the retromolar bone remodelling was only tested in the non-growing adult sample.*

### Revision (verb nominalisation)

*However, these results may have been **limited** by the current CBCT resolution to accurately delineate the maxillary cancellous bone. Another **limitation** was that the retromolar bone remodelling was only tested in the non-growing adult sample.*

## Notes

Usage of the noun *limitation* is an effective example of thematic word echo to the verb *limited*.

## Summary

Overall, the backtracking induced by an inter-sentence pronoun or synonym can be revised by replacement with an explicit but not redundant form of the antecedent (e.g., abbreviated or modified). Another revision option is to emphasise (e.g., enumerate) the antecedent to facilitate the backtracking.

The revision options for inter-sentence backtracking are similar to those for intra-sentence backtracking. However, because of the increased antecedent-referent distance, the rhetorical distraction is more impeded immediate comprehension than dissonance.

Synonymy is inconsistency.

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*Questions or comments about distracting syntax will be responded to, possibly in a subsequent column.*

# Medical Devices

## Medical devices – here we come!

The spring EMWA conference held in Barcelona is now behind us – and what a conference it was for medical device writers and those who want to become one! A full symposium day on medical devices with more than 200 registrants and two fully booked medical device workshops showed the interest and need for further training and information on this type of medical writing. Plenty to do for the MD-SIG group who met during the conference to brainstorm on future EMWA offerings such as workshops, webinars, and expert seminar series.

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## “Medical Devices and Technologies – Emerging Opportunities for Medical Communicators”

The 6th EMWA symposium day was for regulatory writers and medical communicators alike, and aimed to provide the perspectives of different stakeholders, including representatives from the European Commission, notified bodies, medical device companies, patient organisations, reimbursement professionals, and lastly medical writers themselves. There was an interesting mix of medical writing experience in the auditorium with approximately a third having less than 2 years of experience, and another third with more than 10 years. This most likely reflects the desire of newcomers to embark on a new field with good job opportunities and the desire of experienced writers to explore new horizons, after perhaps feeling overly comfortable in their area of expertise.

Claudia Frumento kickstarted the day by giving an introduction to the fascinating world of medical devices. Did you know that Ancient Egypt already used medical devices? Aside from medical device classifications and regulations, Claudia also highlighted the pros and cons of writing for medical devices as compared to pharma. Some of the pros for medical device writing were business opportunities, more long-lasting relationships with medical device companies, and the fast pace, with constantly new devices being developed (the time pressure associated with the fast-paced environment was added to the “cons box”).

Gillian Pritchard elucidated on medical writing skills acquired in pharmaceuticals that are transferrable to medical devices. In a nutshell: “Yes, you can” use many transferable skills. If you are considering a transition from pharmaceuticals to medical devices, check out her symposium presentation which is available on the EMWA website. It is also a useful reading material when

preparing yourself for an interview with medical device companies.

Another highlight of the morning was having Paul Piscoi as representative of the European Commission present the medical device regulations. Paul has agreed to have his full presentation available on the EMWA website. If you are working in regulatory medical device writing or considering embarking in this field, this presentation is a must! The sheer volume of all the new guidance documents to come seems daunting at first, but having direct access to first-hand information is extremely valuable.

After the view of the European Commission, Itoro Udofia, head of the notified body, Underwriters Laboratories, gave an insightful talk about what notified bodies are looking for in Clinical Evaluation Reports (CERs). Itoro transformed the complex new regulations in an easily digestible and delightful presentation. “One picture is saying more than 1,000 words” – he explained the increasing scrutiny of the new regulations in relation to the risk of the device with just one simple graph. Importantly, Itoro reminded us of a vital skill a medical writer should have – to know and write for your target audience. And – are you aware of the job opportunities available at notified bodies?

It was impressive to see also the amount of work that goes into the implementation of the new regulations from the side of the European Commission and Notified Bodies, with a lot of effort put in educating people. During the panel session, led by Jane Edwards, Head of Global Communications at the notified body BSI, the audience used the opportunity to ask plenty of questions that led to a lively and interesting discussion.

While the morning session provided a solid

foundation on medical devices and the associated regulations, the afternoon session touched on diverse areas within this field. Following the EMWA symposium tradition of presenting a 360° view, Kyle J. Rose spoke as patient representative of the International Diabetes Federation (IDF). Hearing the patient’s voice is important as we should constantly be reminded that our work ultimately affects patients’ safety. Aside from providing an insight about living with a chronic disease, Kyle talked about one of his areas of expertise, apps, that can be classified as medical devices. In particular, Kyle was involved in authoring the IDF position paper on medical device apps. During the talk as well as during the discussion thereafter, it became obvious what a complex situation the fast-paced environment of apps is, e.g., when is a software update a significant change? What to do if an app is generated by people who might not even know they have developed a class III medical device? Certainly a topic that would need its own symposium.

Ivan Krstic of Elsevier presented on how to use Embase for medical device systematic reviews. The new MEDDEV 2.7.1/Rev 4 guideline on writing CERs does not accept PubMed as sole resource of literature, and rather requests additional databases such as the Cochrane Central Register of Controlled Trials or Embase. The guideline also requires that CER authors are trained on literature searches on PubMed or Embase. If you have attended the symposium – this checkbox is ticked! Certainly, Embase can also be used for all types of systematic literature searches, allowing for broader as well as narrower searches.

On the case example of a bioresorbable scaffold, Myriam Stieler from Biotronik showed



During the symposium, it became obvious what a complex situation the fast-paced environment of apps is, e.g., when is a software update a significant change?

the full life cycle of a product. She discussed the first considerations to building a prototype, the preclinical tests including bench and animal testing, the first clinical studies, the need for re-design, the CE-mark process, and the possible pitfalls thereafter. The potential impact of the learning curve, both, on how to best implant the device, as well as the competence of the individual operator, need to be considered. Post-market follow-up data are paramount to monitor the safety of a new implantable technology and to ensure that the roll out of a new implantable technology into clinical practice is safe. For instance, some late-emerging issues were observed with a competitor's bioresorbable scaffold which were only detected during post-market follow-up. As these issues were also related to the implant technique, implantation recommendations were published along with a proctoring programmes to assure patient safety. In summary, it is very important to understand that, in contrast to pharmaceuticals, the safety and performance of an implantable device also depends on the implanter.

Patrice Becker presented publication planning at Medtronic, one of the largest medical device companies. He highlighted the challenges and necessities of publishing preclinical studies and the challenges of the fast-changing world of

medical devices. Once the primary study endpoint is reached and data are published, devices are often close to being outdated as the life cycle of a product is so short. Therefore, sound publication planning is paramount. Very useful were his slides related to timelines for individual tasks, e.g., before a conference abstract submission deadline. Myriam and Patrice both closed the loop to the new regulatory requirements for more clinical study data where (at least for the class III devices they are working on) it is in the manufacturer's interest to have sufficient preclinical and clinical evidence because physicians will only consider using products supported by convincing clinical data.

Oleg Borisenko, one of the few experts with an overarching knowledge on medical device reimbursement, was able to provide an introduction to market access in Europe and the associated documents for medical writers in only 30 minutes. Especially helpful were his tips on how to prepare for writing market access related documents – even though getting familiar with this landscape seems to be a giant task! Certainly, everybody interested in reimbursement and market access should take the time to read his presentation thoroughly and follow the recommendations he provided. Despite the complexity and novelty of the topic, there was a

lot of interest from the audience and Oleg proved his expertise by answering all questions succinctly and clearly.

The talks were followed by a panel discussion with active participation from the audience, including questions on US medical device regulations, harmonisation of regulations, as well as the current political situation, i.e., potential implications of Brexit.

We hope that those who attended the symposium had an enjoyable, fruitful and thought-provoking day. We also look forward to reading the symposium report from our "medical device newbies" which will be included in the conference report in the September issue. If made available, the symposium presentations have been uploaded to the appropriate section of the EMWA website.

A huge thank you to the presenters as well as to the audience for asking plenty of questions which helped to make the symposium a success!

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# Getting Your Foot in the Door

## Editorial

Landing the first medical writing job is not easy. Clare Chang's contribution describes her journey, the challenges she faced, and the different measures she took to overcome these hurdles.

EMWA is very much aware of these challenges, as addressed at the 3rd Annual Internship Forum at the Spring Conference in Barcelona. Outside of the Spring Conference, EMWA members as part of the Ambassador Programme continue to spread the word about medical writing by giving presentations at educational institutions, careers fairs, and other events.

Raquel Billiones

## SECTION EDITOR



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## Paving the path towards medical writing

*Reading is like breathing in, writing is like breathing out.*

– Pam Allyn

My love affair with books and writing stemmed from childhood years before I could even begin to comprehend my obsession. I wrote essays, songs, and blogs. The eloquence of writing – the way words dance on paper to paint beautiful imageries – has always been something that mesmerised me. However, there is also a rational side to me, one that is hungry for the way the world works with a spot of altruism. This is the side that propelled me into the world of science.

Starting right from the basics, understanding the building blocks of life, all the way to uncovering mechanisms and developing compounds to treat diseases, I chased relentlessly after degrees that would signify my expertise. Despite my thirst for knowledge, I did not forget my other passion. During my master's programme, I started to freelance as an editor, translator, and writer for clients from various scientific backgrounds and businesses. Curiously, this side job of mine ignited an idea during my PhD training: How can I combine writing with my love for science while translating research into the societal dimension?

As I embarked on my new quest, my career counsellor at Aarhus University introduced me to a medical writer. I remember what resonated with me was that medical regulatory writing wasn't just about writing; in fact, it stood at the crossroads of project management and consultation. To me, this was a relief! Although I enjoyed constructive

aloneness, I also relished in constructive discussions and collaborations. During this time, I also tried to find more resources related to medical writing. I especially liked the book *What Every Medical Writer Needs to Know. Questions and Answers for the Serious Medical Author* by Robert B. Taylor. Not only does it describe the work medical writing entails, it also discusses the personalities of medical writers and provides pointers on how to increase one's visibility to enter the medical writing world.

As the end of my PhD training loomed closer, I decided to start my job search 6 months before the hand-in date.

I managed to get an interview a month into my job search. I went for the on-site interview; 2 months later, they responded to me with a "no". When I asked for feedback, they said that it was because I lacked collaboration and conflict resolution skills. I moped over this for about 2 days, then proceeded to concentrate on writing my thesis. Fast-forward 2 months, I completed

my thesis in August and started to think about the hiring manager's response. I thought that

I needed her to know that I had collaboration and conflict resolution skills so I wrote an email to her and gave her three scenarios that depicted

The eloquence of writing – the way words dance on paper to paint beautiful imageries – has always been something that mesmerised me.



Clare (Chi Chih) Chang

both skills. A week later she told me that there was a new job posting and that I should apply for it (which of course I did).

As my job search grew more desperate, I remembered coming across the Cheeky Scientist Association (CSA), which helps academics transition into industry. I did not know anyone who used their services, but I decided to take a leap of faith and joined the CSA. The focus of the CSA was to help academics understand industry lingo, etiquette, and goals, with a focus on networking. I then realised that the only reason I managed to get the

first interview was due to the aforementioned mentor, who acted as my referral.

I was then contacted for a job interview in mid-September but was informed that they were not going to take it further – this time it was because I did not have project management skills and I did not show enough interest. This time I was rather annoyed because I knew that project management is one of my top skills. So, I wrote another email to the human resources (HR) department to address these two issues. Two

days later, HR replied and said they would like to give me the second interview. This time I was really worried because I thought that I was just really lousy at interviews. I booked our university career counsellor to ask her for interview advice. I read as much as I could about what to do and came up with numerous answers in response to possible interview questions. I also prepared for the interview using the STAR (situation, task, action, result) technique.<sup>1</sup> Personally, I thought the interview went really well. I even met the vice president and our interview went overtime, too. However, they still decided on another candidate.

Through all of this I have also been in contact with recruiters and HR personnel from other companies (over 20 interviews). However, obtaining a work visa was always an issue – I'm

from Taiwan and I have been looking for medical writing positions abroad. It has been a difficult experience so far, but I must say, attending networking events, cold contacting interesting professionals on LinkedIn (more than 50), and the interviews have all given me insight into the lives of medical writers at different types of companies (for example, CRO vs. pharmaceutical companies, and large vs. mid-size companies). Additionally, learning more about clinical development via online courses, studying the ICH guidelines, and more recently, joining EMWA, AMWA and other professional networks, have helped me solidify a foundation in regulatory documents and guidelines that writers use. Finally, I joined Toastmasters to develop public speaking and leadership skills, which will prepare me for times when I will have to face clients and talk during roundtable meetings. Amongst the numerous defeats, I have slowly found ways to overcome each obstacle, while learning more about the regulatory world and myself. I am currently developing a blog to document my development, provide resources for other aspiring writers, and showcase my writing. Hopefully, these bricks will pave a path towards regulatory medical writing.

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**Save the date:**  
**EMWA Conference**  
**WARSAW**  
**Nov 8-10, 2018**  
 For more information:  
<https://www.emwa.org/conferences/future-conferences/>

## The EMWA Ambassador Programme

We have initiated the Ambassador Programme as part of EMWA's strategy to raise awareness about the medical writing profession and the benefits of joining our organisation. The goal of the programme is to recruit experienced EMWA members to give presentations at university career events, professional training organisations, and medical conferences. So far we have made a good start.

On October 19, 2017, Abe Shevack, then EMWA President, gave a talk at the National Congress of Clinical Research in Bucharest, Romania. This gathering included 200 professionals from the Romanian health and education authorities, pharmaceutical companies, CROs, medical students, and clinical investigators. This was the first time that a representative from EMWA had given a talk in Romania. On February 22, 2018, Abe addressed a group of over 30 PhD students at the PhD Winter School of the Leibniz-Institute for Molecular Pharmacology in Berlin (Buch). The feedback was positive with a number of the participants mentioning that they had never heard of medical writing before.

EMWA Vice President Tiziana von Bruchhausen has also given two presentations on medical writing and EMWA. The first one was in Rome on January 16, 2018, at Alfa FCM for a group of 30 young physicians working in medical research. On March 9, 2018, Tiziana gave another talk at the Dr Notghi Academy to a group of trainees in clinical development in Berlin. Both sessions went well and have opened the way to future collaborations between our organisations.

EMWA Past President Alison Rapley has given two presentations on medical communications and EMWA. One was at the Biosciences Day at Reading University on January 31, 2018, to 30 students at the Young Biologists Forum of the Royal Society of Biology. She also presented a career talk to 40 students and an interactive course on medical writing skills on March 6, 2018, at the University College, London, during the university's Insight into Health and Life Science Careers Week. This talk was com-

pletely booked within a day of advertisement.

Raquel Billiones, Past EMWA Honorary Secretary, delivered a talk on careers in medical writing at the Zurich Life Science Day organised by the Swiss Federal Institute of Technology (ETH) and the University of Zurich on February 1, 2018. The audience was composed of PhD students ( $\approx 50\%$ ), postdocs ( $\approx 30\%$ ), MSc and BSc students ( $\approx 20\%$ ), and young professionals ( $\approx 10\%$ ). As of this writing, Raquel is scheduled to present two talks on behalf of EMWA on April 19, 2018, at the MedTec Europe 2018 in Stuttgart, Germany. One presentation is titled *Introduction to EMWA and the Role of Medical Writers in the Medical Devices Industry*.

Also at the time of this writing, Anne McDonough is scheduled to give a talk at Anglia Ruskin University – Faculty of Medical Sciences and Public Health Careers Day at their campus in Essex on April 18, 2018.

Scheduled next is a joint presentation by Raquel and Abe at BioM (Munich Biotech Cluster) on July 5, 2018, in Munich. The 1-day event targeting biotech companies and start-ups will cover the following topics:

- Introduction to the Role of Medical Writers in Clinical Trials and the Drug Development Process
- Managing the Clinical Study Protocol Writing Process
- The Clinical Study Report Development Process
- Transparency and Disclosure

EMWA wants to keep the momentum going and to participate in as many of these events as possible. We are currently searching for experienced speakers to take part in this programme.

We kindly request that members get in touch with us if they, or perhaps someone they know, would be amenable to giving such presentations. For more information, please contact the Head Office ([info@emwa.org](mailto:info@emwa.org)).

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# Out on Our Own

## Editorial

Greetings, readers.

Networking is a key tool for running a successful freelance business. As business owners, freelancers not only have to interact with clients, but also seek to develop professional networks with other colleagues. The chief advantage in the latter is that it offers an opportunity for exchanging tips, sharing experiences, increasing client portfolio, as well as collaborating. The biannual EMWA conferences, especially the Freelance Business Forum, are indeed fantastic platforms to do this. However, such face-to-face networking is an activity that has to be considered in light of investment – of time, of money, of effort – and the question is how to engage in effective networking without making a huge investment. In this issue of OOOO, Peter Llewellyn, the Managing Director of NetworkPharma Ltd and a networking leader in medical communication circles, offers a possible solution. Towards the end of 2017, Peter started organising weekly web-based meetings for MedComms Workbook subscribers to log in and participate in group discussions. In his article, Peter

discusses his idea and presents testimonials from freelancers who have participated in these online networking events.

The medical device industry is growing in leaps and bounds. Indeed, the symposium at the recent EMWA conference in Barcelona dealt with medical devices. In addition, two of the workshops held at the conference offered attendees an insight into the various regulatory guidelines and laws regarding evaluation and approval of medical devices in the European Economic Area. These developments offer another vast area for medical writers, including freelancers, to be of service. Gauri Jawdekar-Abraham, a freelancer based in Germany, shares with us her story on how she serendipitously got in the field of writing for medical devices, her becoming a freelancer, and what opportunities and challenges she foresees in her journey as a medical device writer.

I hope you will enjoy these articles.

I would also like to inform you that this will be my final editorial for OOOO. Since November 2015, I have had the pleasure and privilege of helping our contributors publish their articles...nay, their experiences, their

thoughts, their ideas...their stories, in OOOO. These were the stories, shared by those who went down the freelance path much before me, that I found useful when I started my freelance business in Germany. I am sure many others as well have found the OOOO as a useful guide. As an editor, I read these stories first-hand, and they always served to tell me that while we freelancers come from all sorts of diverse backgrounds, we are all alike in that we are adventurers. I am glad I had the opportunity to serve the OOOO and it is time now for me to pass the torch on to Laura Kehoe, a fellow Freelance Business Group subcommittee member. Laura is an experienced editor, having been with the journal Hepatology for a number of years before starting her freelance business. I am sure Laura will bring more to OOOO, starting with the September issue, and I wish her the very best.

Many thanks to our brilliant editorial staff for all their help with publishing OOOO and above all, thank you for submitting your articles which make OOOO such a wonderful read.

Satyen Shenoy

## Opening up the room

“If you put interesting people together in a room then interesting things happen.” I’ve been running MedComms Networking community activities ([www.MedCommsNetworking.com](http://www.MedCommsNetworking.com)) for more than 11 years and this has always been my mantra. We have proven it many times now, and the same will be true of organisations like EMWA. But what defines the “room” these days?

I would argue that real-life, in-person meetings always offer the most opportunities for those interesting things to happen, but they also present many challenges especially, dare I say it, for freelancers. You’re busy. The cost of attending events can be prohibitive. Even if the events (like the MedComms Networking events) are free to attend there is still the cost of travel, and the opportunity cost – you could be working more billable hours instead. Or you might be working from your boat in the Caribbean, where there aren’t too many relevant meetings taking place for



medical writers. But in practice, wherever you are based, the odds are that the meeting you really want to attend is never just around the corner at a time when you have nothing else to do! What about the kids? The puppy? The pottery classes?

Didn’t you become a freelancer to gain more control over these varied aspects of life?

Well, yes. Though I would also argue that as a freelancer you need to recognise you are now running a small business. You are not just a writer

now. You're the IT department, the accounts department, the sales and marketing department, the training department, and much more besides. A business requires investment of time and money to succeed. That must surely include time spent learning from others, meeting prospective clients and collaborators, and – importantly in my opinion – allowing yourselves the opportunity to think outside your box. How else do you develop yourself and your business?

For a couple of years now, I have been running the MedComms Workbook subscription service for freelancers who work in and around medcomms ([www.MedCommsWorkbook.com](http://www.MedCommsWorkbook.com)). Whilst that includes sending out work opportunities, I don't find that the most interesting aspect. What interests me most is how we can facilitate education, networking, support, and collaboration amongst those subscribers so their businesses thrive.

I run regular events in the UK where freelancers can meet and chat face-to-face, and I have tried very hard to encourage individuals to organise their own informal local gatherings, but we're constantly facing those challenges we have already identified. So, can I use technology to add another dimension and open more opportunities?

I was sceptical. My experience to date had not been inspiring. I knew the technology was out there, but too often it didn't really work or it required much more money or resource than I had to do it properly. But at the end of last year I started playing with Zoom meetings ([www.zoom.us](http://www.zoom.us)) and my opinion changed. If we aren't at a tipping point yet then we are very close, and the potential benefits are significant.

I now run a weekly video-based meeting I refer to as a "virtual coffee morning", for subscribers to the MedComms Workbook service. The rest of this article will read like an advert for Zoom so I should make it clear I am simply a customer. I have no stake in their service and I'm sure there are other similar services – I just haven't found anything that works quite so well, so easily, and so inexpensively. What interests me mostly, though, are the principles it demonstrates for working smarter, more than the specific platform itself. And how such easily accessible technology is now offering real advantages for groups of remote workers. Well, like freelance writers wanting to network.

So, I asked some of the subscribers to the MedComms Workbook service what they think

and they articulated the benefits so much better than I could.

*Working in your "own bubble" can limit your horizons and close your eyes to developments in medcomms that have not yet touched you. It is sometimes easier to shy away from networking opportunities that may challenge your view on things. You just can't appreciate the benefits of sharing experiences, knowledge, and ideas in a safe environment until you give it a go. Don't be put off by corporate speak or hyperbole about networking. At its core is the common sense of getting together to chat about how working could be better; technology transforms this to broaden the reach to a diverse range of people you would never have the opportunity to meet otherwise.*

**Susanna Ryan, Medical Writer, UK**

*I think Zoom works beautifully. It's a lot less effort to follow what is happening than a teleconference. For me, these drop-in virtual coffee mornings provide reassurance and advice about handling business problems and ideas on making the most of opportunities available for editors.*

**Petra Roberts, Medical Editor, UK**

*I've found the Zoom meetings really useful in expanding and strengthening my network. I'm not able to join in every week, but I have found it useful when I do find the time to join the meetings, and I've always come away with some useful information and new contacts. It really helps to know that there is a community and we can help each other with tricky situations or celebrate achievements.*

**Jen Lewis, Medical Writer, UK**

*I've been able to hear perspectives/experiences from other freelancers (with diverse career backgrounds), which I've found really valuable. It's always reassuring to hear how other freelancers have managed similar situations to those that I've encountered. It's easy to become isolated when working as a freelancer, so this is a great way to bring the freelance medical writing/communications community closer together, and to learn from each other."*

**Howard Donohue, Medical Writer, UK**

*The Zoom coffee mornings are a great chance for me to chat with and share experiences with my fellow freelancers. I have found the Zoom platform very easy to set up and use, and I look forward to our regular meetings.*

**Mina Varsani, Medical Writer, UK**

*I've found the Zoom MedComms meetings to be a proactive practical way of discussing some of the practical everyday financial and business challenges of freelancing. It's good to see and hear first-hand opinions from real people live on screen, rather than just reading these online. You realise you're not the only one facing these challenges. I've picked up some valuable tips, names and solutions for my current and future freelance business. Plus, it's a great way to meet peers and potential clients without leaving your office.*

**Corinne Swainger, Medical Writer, UK**

*What I appreciate about the Zoom meetings for freelancers is to see the international perspective of similar challenges and different solutions in different counties for freelancers. Another benefit is that it is simply fun to meet different colleagues in different countries once a week. Freelancing can be lonely sometimes.*

**Kris Overby, Medical Writer/  
Editor, Sweden**

*I think that Zoom is a fabulous initiative, particularly for inter-country contact. As a freelancer, it's sometimes hard to justify using potential working hours to network, but I think this is a personal objective some of us should probably work on.*

**Amy Whereat-Terdjman,  
Medical Writer, France**

*Zoom meetings with several other MedComms Workbook subscribers have been packed with practical advice, and a refreshing reminder that I am not alone in my diverse freelancing concerns. Although Zoom meetings do not replace face-to-face networking, this is certainly the next-best approach in my opinion.*

**Gladriel Bonnel,  
Medical Writer, France**

*As a freelance medical writer who is working from a yacht while travelling, I am delighted to have the opportunity to take part in the Zoom meetings. Due to living and working this way, I have zero opportunity to network face-to-face with other freelancers, so I am finding the discussion about general and specific issues related to the freelance business environment really helpful. Plus, it is good to put faces to names and learn a little bit more about what is going on in the lives of other freelancers. I am definitely feeling more connected to my fellow*

*freelancers – and aware of important issues relating to freelancing – since attending the meetings.*

**Sarah Smith, Medical Writer/  
Editor, currently on a boat in Martinique**

So yes, even a freelancer based out in the Caribbean can now join in and catch up on the gossip and learn from her peers and gain from the professional support that comes from having a supportive network. Using Zoom we not only have informal conversations, but also can share screens to collaborate on projects, present

training talks, involve guest speakers and much more. As for the technology – if I can do it now, anyone can. Give it a go yourself with your own network. There really is no need to feel isolated.

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## Finding my way in the world of freelancing – *in vitro* medical devices

### My foray into freelancing

As clichéd as it might sound, I am a true believer in grabbing opportunities. I also firmly believe in creating opportunities for myself. When I embarked upon my trans-Atlantic journey from Los Angeles to Germany 7 years ago, little did I foresee myself considering a career in medical writing, let alone in the *in vitro* diagnostic (IVD) medical device sector. However, when a series of events presented me with the opportunity to write for IVD medical devices, I grabbed it. It has been a satisfying change. There was a big learning curve. The IVD sector, which is classified under medical devices, is an industry in itself. I got to see first-hand the need for qualified writers to communicate product-related material in a precise and articulate way. The power of communication is also reflected in software designs, which needs to be easy to understand and yet have an aesthetically pleasing appearance.

After a change in circumstances, I transitioned into freelancing, already armed with a client. This gave me an opportunity to work across a range of IVD devices instead of writing for just one product line. I was able to work with multiple clients ranging from mid-sized to big companies. So far there are no regrets from a change in career. I enjoy the flexible working hours, especially while caring for a young family.

### Opportunities

IVDs have become crucial for providing information that is necessary for making clinical decisions and managing diseases. The German IVD market is dominated by small and medium-sized companies. Frequently they lack dedicated



teams or departments to write medical communication or regulatory documents. In such instances, the work needs to be outsourced, thus providing opportunities for freelancers. 2018 is an especially exciting time for medical writers. On the one hand, they are being recognised as professionals,<sup>1</sup> and on the other hand, there is a need for generating a range of technical documents, especially due to a significant change in the EU regulations for IVD medical devices.

The new IVD Regulation, (EU) 2017/746 (IVDR),<sup>2</sup> which was published in May 2017, provides a 5-year transition period for manufacturers of IVD devices to implement the necessary changes. This is challenging because it requires a complete change in the mindset of how

things were done before the IVDR came into place. For example, under the old 98/79/EC In Vitro Diagnostic Medical Device Directive (IVDD),<sup>3</sup> manufacturers were responsible for ensuring that their products, with the exception of some devices, comply with the essential requirements of the directive before affixing the CE marking. However, under the new IVD regulations, manufacturers will be unable to do so. Instead they will require a notified body to certify their products for them. Overall, the number of regulatory documents to be completed will increase.

Another example of an opportunity for medical writers is the impact that the new regulations will have on the overlap between the IVD and pharmaceutical industries. IVD medical

devices known as companion diagnostics (CDx) are used for personalised medicine (also known as precision medicine) to ensure the right therapy for the right group of patients at the right time.<sup>4</sup> With the new risk-based classification, CDx will fall under class C, the second-highest category. CDx is defined as: *[an] IVD device which is essential for the safe and effective use of a corresponding medicinal product to:*

- Identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- Identify, before and/or during treatment, patients likely to be at a risk of serious adverse reactions as a result of treatment with the corresponding medicinal product<sup>5</sup>

Often medicinal products and CDx are developed independently following different schedules and regulatory requirements. They are paired with each other only towards the end of the development phase. This approach leaves a gap in the process of obtaining evidence and validations. More cooperation between the pharmaceutical and IVD industries will be required to co-develop the medicinal product and CDx. Synergistic business models will be seen in the future to enable simultaneous review and approval of both the drug and CDx.<sup>6</sup> Consequently, medical writers will be required to prepare and coordinate regulatory documents for both.

### Challenges as a freelancer and the way forward

After talking with other freelance writers, I realised that my journey to freelancing has been a bit unconventional because it started relatively

quickly in my infant medical writing career. The norm is to first work for companies or clinical research organisations, gather significant writing experience, and then branch out on your own. So, I find myself in a bit of a chicken-and-egg conundrum: How do I find more clients and how do I get more experience? Neither one seems possible without the other.

Instead of heading towards a downward spiral in trying to solve this conundrum, I created my own action plan – invest in experience and keep networking. Organisations such as EMWA have given me the perfect platform to implement that plan. The diverse workshops offered in the EPDP training programme have helped me to expand my medical writing skills. Interacting with members of EMWA and the Freelance Business Group has been an incredible way to learn from their experiences.

This definitely helped and will help me to move forward, albeit with a bit of uncertainty in getting further clients on board. Irrespective of how one starts out on their own, everyone is faced with a unique set of opportunities and challenges. The best way to take chances and overcoming challenges is by not giving up.

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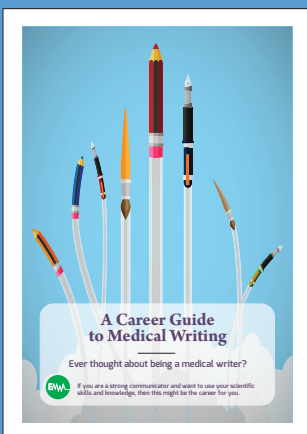
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## EMWA's Medical Writing Career Guide

### Included in the guide:

- What is medical writing
- The different types of medical writing
- The skills and qualifications needed to be a medical writer
- Where medical writers work and what they do
- How to get started
- How much to expect to get paid
- Career prospects for medical writers

Download at: <https://www.emwa.org/resources/useful-reading/a-career-guide-to-medical-writing/>

# Upcoming issues of **Medical Writing**



**September 2018:**

## **Editing**

This issue will cover micro- and macro-editing, quality control, software for editing, and how to manage collaborative editing.

**The deadline for feature articles is June 11, 2018.**



**December 2018:**

## **Patient-reported outcomes**

Patient-reported outcomes are outcomes reported by the patient rather than by healthcare professionals. This issue will include articles on their design, quality, feasibility, analysis, use, and future.

**The deadline for feature articles is September 10, 2018.**



**March 2019:**

## **Careers in medical writing**

By choice or by chance? Medical writing work is very diverse and so are the careers of people in this field. This issue will focus on stories about medical writing careers.

**The deadline for feature articles is December 10, 2018.**



**June 2019:**

## **Generics and biosimilars**

This issue will introduce readers to generics and biosimilars; provide and discuss their key legal and regulatory aspects in the US and Europe; and discuss their economics and how they affect pharmaceutical companies.

**The deadline for feature articles is March 10, 2019.**

### **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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