

Volume 27 Number 1  
March 2018

# Medical Writing



## Vaccines & immunotherapies

### Also in this issue...

- Results of the 2017 EMWA salary survey
- Lay writing: Strategies for improving assent forms for children and adolescent participation in health research
- The perils of the unknown: Missing data in clinical studies
- Medical writing in China: Trends and opportunities
- PhD student: A medical writer in the making!
- **New section: Medical Devices**



EUROPEAN MEDICAL WRITERS ASSOCIATION



EUROPEAN  
MEDICAL  
WRITERS  
ASSOCIATION

**Medical Writing** is the official journal of the European Medical Writers Association (EMWA). It is a quarterly journal that publishes articles on topics relevant to professional medical writers. Members of EMWA receive *Medical Writing* as part of their membership. For more information, contact [mew@emwa.org](mailto:mew@emwa.org).

#### Submissions:

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

#### Editor-in-Chief

Phillip Leventhal

#### Co-Editor

Stephen Gilliver

#### Associate Editors

Anuradha Alahari  
Raquel Billiones  
Barbara Grossman  
Joselita T. Salita  
Nathan Susnik  
Katharine Webb

#### Section Editors

Laura Collada Ali  
Lisa Chamberlain James  
Beatrix Doerr  
Karin Eichele  
Claire Gudex  
Wendy Kingdom  
Maria Koltowska-Hägström  
Alison McIntosh  
Hervé Maisonneuve  
Greg Morley  
Simon Page  
Satyen Shenoy

#### Copy Editor/Reviewer

Amy Whereat

#### Managing Editor

Victoria J. White

#### Editor Emeritus

Elise Langdon-Neuner



**Editorial: Vaccines and immunotherapies** 1  
Trevor Stanbury

**President's Column** 2

**A history of EMWA** 3

- The early years
- From 2008 to 2017

**EMWA News** 6

### Feature articles

**An introduction to vaccines and immunotherapies** 7

Jonathan M. Pitt and Julie Harriague

**Immuno-oncology: Harnessing our immune system to fight cancer** 11

Anne Rasclé and Trevor Stanbury

**Changing methods to access targeted therapies in oncology** 18

Trevor Stanbury, Xavier Paoletti, and Bernard Asselain

**HIV vaccine clinical trials: An overview** 23

Jackline Odhiambo

**Allergen immunotherapy in the European regulatory environment** 30

Ulrike Lehnigk

**Pharmacovigilance for vaccines and immunotherapies: What does the medical writer need to know?** 35

Justina Orleans-Lindsay

**Addressing vaccine hesitancy in writing** 39

Michelle Guillemard

**Results of the 2017 EMWA salary survey** 43

Ansgar Dressler, Julia Forjanic Klapproth, and Andrea Rossi

**Lay writing: Strategies for improving assent forms for children and adolescent participation in health research** 51

Danielle Yuill, Rachel Barron, and Jennifer Preston

**The perils of the unknown: Missing data in clinical studies** 56

Helen Bridge and Thomas M. Schindler

**Medical writing in China: Trends and opportunities** 60

Yanni Wang

**PhD: A medical writer in the making!** 64

Somsuvro Basu

### Regular features

**News from the EMA** 68

**Medical Communications** 73

- Readability of biomedical research articles: Where are we now, and how can we move on?

**Journal Watch** 76

**In the Bookstores** 79

- *Plain English for Doctors and Other Medical Scientists*

**Webscout** 80

**Lingua Franca and Beyond** 82

- How to make your scientific paper easier to read

**Teaching Medical Writing** 84

- Learning to write a good story: Academic writing for qualitative health researchers

**Good Writing Practice** 87

- Inter-sentence discontinuity 2

**Medical Devices** 90

- EMWA's Medical Device Symposium: Medical Devices and Technologies Emerging Opportunities for Medical Communicators

**Getting Your Foot in the Door** 93

- Bridging the gap between industry and academia - Life Science Zurich Young Scientist Network

**Out on Our Own** 95

- The Freelance Business Forum in Cascais
- The elusive journey from nurse to medical writer
- Bloody shoes to barefoot: Perspectives from a South African medical writer

# Medical Writing

## Vaccines and immunotherapies

The use of vaccines and immunotherapies in medicine dates back to the end of the 18th century and the work of Edward Jenner, the father of immunology. Jenner, building on the observations of John Fewster in 1768, showed that inoculation with the cowpox virus prevented smallpox. Thus the first vaccine, the name derived from the Latin for cow, “vacca”, was developed.

Although Jenner’s discovery is thought to have saved more lives than any other scientific discovery, the use of vaccines has mostly been limited to preventing childhood disease (including measles, tetanus, diphtheria, etc.). Today, with a better understanding of the immune system, vaccines and immunotherapy provide hope for treating other diseases. Despite having developed many strategies to attack disease, we have largely ignored the power of our own immune system. Harnessing the immune system’s capacity, combined with the arsenal of therapies already developed, may allow us to advance in the war against a variety of diseases.

In this issue of *Medical Writing*, we discuss various aspects of the development of vaccines and immunotherapies. **Jonathan M. Pitt** and **Julie Harriague** open the issue with an introduction to the topic. **Jackline Odhiambo** in her article, “HIV vaccine clinical trials” discusses the number of challenges involved in developing the elusive HIV vaccine, with the potential of saving millions of lives. **Ulrike Lehnigk** in her article, “Allergen immunotherapy in the European regulatory environment”, gives an overview of allergen immunotherapies and the current regulatory constraints. In “Immuno-oncology: Harnessing our immune system to fight cancer” by **Anne Rasclé** and me, we briefly describe the mechanism by which cancer suppresses our immune response, the different immunotherapies being developed, and how clinical study design has evolved to evaluate these agents. Since vaccines and immunotherapies target the immune system and not disease, the traditional methods used to evaluate efficacy and toxicity need to be adapted. In the article, “Changing methods to assess targeted therapies in oncology”, adapted from a French article by **Bernard Asselain** and **Xavier Paoletti**, we describe the method-



**Figure 1. The Cow Pock.** In this cartoon, which suggests “the Wonderful Effects of the New Inoculation!”, cows are depicted as emerging from people’s bodies after being administered the cowpox virus.

ological and statistical changes made to evaluate targeted therapies, including immunotherapies. The use of vaccines and immunotherapies are not without safety concerns. **Justina Orleans-Lindsay** in her article, “Pharmacovigilance for vaccines and immunotherapies: What does the medical writer need to know?” gives us insight into the specific adverse events and regulatory framework in this area. Since the development of the smallpox vaccine by Jenner, vaccination has always been shrouded by controversy (Figure 1, attributed to British satirist James Gillray). **Michelle Guillemard** in her article, “Addressing vaccine hesitancy in writing” describes the importance of clarity combined with other strategies when writing about vaccines.

I hope you find this issue of *Medical Writing* interesting and that it will provide a framework for understanding the current developments in vaccines and immunotherapies, and the specific challenges involved.

**GUEST EDITOR**  
 **Trevor Stanbury**  
t-stanbury@unicancer.fr

By James Gillray – Library of Congress, Prints & Photographs Division, LC-USZC4-3147 (color film copy transparency).  
Public domain. <https://commons.wikimedia.org/w/index.php?curid=2289666>

# President's Message



## Dear EMWA Members,

As you are well aware, we have been celebrating our 25th anniversary as an organisation and have sent out specially designed buttons with the December issue of *Medical Writing* to commemorate the occasion. To continue the celebration, we are offering a prize for the most creative picture of the anniversary buttons. So go out and take some photographs. They can be posted on Twitter (@Official\_EMWA) or sent to the Executive Committee for judging. The winners will be announced at the conference in Barcelona.

The monthly EMWA News Blast has been receiving positive reviews from our members who have been receiving these short digests of current news about our conferences, webinars, and information of general interest. We will be archiving all past News Blasts in the members' section of the website.

Our ambassador programme is in full swing. Experienced EMWA members have been featured speakers at university career events and seminars in Europe. Our first speakers have already presented lectures at universities in Reading and Zurich, at clinical development training academies in Rome and Berlin, and at the National Clinical Research Conference in

Bucharest. So the momentum is growing and we are spreading the word about medical writing and EMWA across Europe. If you would be interested in giving an official EMWA presentation, please contact the Executive Committee.

The AMWA-EMWA-ISMPP Joint Position Statement on the Role of Professional Medical Writers in preparing manuscripts for publication has now been translated into Chinese and Japanese. Links to these translations have been posted on the EMWA and International Society for Medical Publication Professionals websites. We have now completed the first planned translations, but more are to follow in Romanian, Hungarian, and Portuguese in order to publicise this important document among non-native English speakers.

The results of the current EMWA salary survey (last survey published in 2012) are now available and appear in this issue of *Medical Writing*. As you may remember, the survey took place between April 7 and May 31 last year. Altogether, 317 members responded. One very interesting result is that salaried employees and freelance writers who hold EMWA Professional Development Programme certificates earn more than those without. This is very encouraging news since it shows that the EMWA educational programme is helping our members to increase their potential value to employers and clients.

Our next conference will take place in Barcelona May 1–5 and features a comprehensive EMWA programme with 50 workshops at the foundation and advanced levels covering a broad range of topics.

Important developments have recently taken place in the field of medical devices in the wake of changes in the European legislation. This has led to an increased demand for medical writers who are knowledgeable in this highly challenging area. We are therefore proud to announce the 6th EMWA one-day symposium on May 3,

“Medical Devices and Technologies – Emerging Opportunities for Medical Communicators”. The symposium is designed for regulatory writers and medical communicators alike and will seek to update participants on the perspectives of legislators, notified bodies, medical device companies, patent representatives, and reimbursement professionals.

In this regard, we have initiated a new special interest group (SIG) on medical devices in order to stimulate future discussions on the latest trends and requirements in this fast-changing field. This new SIG will also develop topics for future expert seminar sessions.

Experienced members will be delighted to hear that we will be offering several Expert Seminar Sessions at this year's conference. The topics will include medical journalism, changes in the guidance for pharmacovigilance risk management plans, orphan drugs and rare disorders, data protection and EMA Policy 0070, clinical trial registries, and clinical study reports for Cochrane reviews.

In addition to all this, we will be offering special early morning seminars that include “Disaster Recovery: A Case Study of a Medical Writing Department's Response to a Cyber Attack”, and two “Full English Breakfast” sessions. As always, we will host the Internship Forum and Freelance Business Forum, as well as an introductory talk on medical writing for new writers, the “Show It and Share It session”, and a variety of social events.

We hope you enjoy reading this very interesting issue of *Medical Writing* dedicated to vaccines and immunotherapies.

I look forward to seeing many of you in Barcelona.

Ens veiem llavors.

**Abe Shevack**

[aspscientist@googlemail.com](mailto:aspscientist@googlemail.com)



# A history of EMWA

## The early years of EMWA

EMWA has now been in existence for 25 years! How is that possible? Time has flown by, and brought with it much change and growth of which we should be proud. This is an opportunity to reflect back on the organisation as it was at its genesis, is today, and has the potential to become in the future. As one who was around in the antediluvian days, this article presents an opportunity to recall the early years and indulge in a trip down Memory Lane. This allows me to cover the early days of EMWA and to fondly recall colleagues whom I now think of as friends, as well as to remember some who are no longer with us.

The primordia of a medical writing group in Europe can be traced back to October 11, 1990, when a group of 14 individuals, representing nine European-based companies, met at the Quorn Grange Hotel in Loughborough, UK, to discuss the possibility of creating a professional medical writing association in Europe. This was before even my time!

In April of 1991, I received a letter from a steering committee representing a collective of European medical writers. They invited me to respond to a questionnaire designed to determine whether there would be sufficient interest to formally establish a European Medical Writers Association. At that time, over 75 people across Europe had voiced interest in such an organisation. Response would drive the effort to convene an inaugural meeting.

It seems that there was enough interest, resulting in a meeting on February 21, 1992, in Brussels. This meeting was attended by 32 people from nine countries, with an interest in forming a professional association. The meeting, chaired by Jane Wynen of SmithKline Beecham, opened with a welcome address by Dr Mike Matthews (whom, I am pleased to note, was an exhibitor at the EMWA 2017 Birmingham conference). Although there were no workshops, there followed a presentation by Dr Helen Frampton on Medical Writing in the Pharmaceutical Industry and my presentation on Enhancing the Reviewability of Regulatory Documents. Following luncheon, the results of the aforementioned questionnaire were discussed, and I then

*EMWA got its start as the European chapter of the American Medical Writers Association (AMWA).*

spoke on behalf of the American Medical Writers Association (AMWA), offering assistance and, perhaps, an opportunity to integrate the European medical writing community into a global association. This was not well received by some in attendance who viewed this as an exercise in “reverse-colonialism”. An ‘energetic’ debate ensued after which a vote was taken. I was surprised and gratified to find that a clear majority (24 of 29) voted to become a chapter of AMWA. An Executive Committee was established, with Jane Wynen as President and Geoff Hall as Vice President, and the European Chapter of AMWA was formed.

It is important to note that the essence of any organisation is embodied in its members. This requires not only that people attend the meetings, but that they volunteer their time and energy to the maintenance and continued evolution of EMWA as a meaningful resource to medical writing professionals. We must continue to build upon the foundations established by those who had the vision and the dedication to create this wonderful organisation and to ensure that it remains a source of value to those in our profession. It is also important to remember some of those who dedicated so much but have left us too soon. EMWA honours two of these individuals through the Geoff Hall Scholarships and the Nick Thompson Fellowships.

Twenty-five years! Quite a milestone! I hope we will continue to cherish and nurture this organisation and continue on for at least another quarter century.

**Art Gertel**  
medscicom@rcn.com



The Newsletter from the European Medical Writers Association  
Chapter of the American Medical Writers Association

Summer, 1993

### AMWA Welcomes its European Chapter

#### A Message from the Chapter President

This past March, the American Medical Writers Association (AMWA) Board of Directors approved the formation of a European chapter, making ours the first chapter outside North America.

provided keys to enhancing the reviewability of regulatory documents. Ceara Roche presented the results of a questionnaire which was sent to 96 people involved in biomedical communication. The function of the questionnaire was to gain basic information on Europe's medical writers and to reveal individual expectations of a European association. Not unlike the AMWA membership, most respondents to the questionnaire were medical writers in the pharmaceutical industry.

## From 2008 to 2014

So much has happened over the years. In 25 years, we have grown from the first 32 attendees in 1992 to more than 1,000 members. EMWA is more dynamic than ever thanks to a large group of volunteers and an excellent Head Office, run by Kingston Smith.

Sometimes it is good to sit back and reflect on the old days and how we are progressing into the future. Geoff Hall wrote a personal and passionate recollection of EMWA's history up to 2007.<sup>1</sup>

Needless to say, the pace of change has increased since then and the history he presented was in need of an update. I am therefore starting where Geoff left off citing the high points of the terms of past presidents and occasionally letting them tell their own stories.

### Julia Forjanic Klapproth (2007 and 2008)

During Julia's term in office the Press Officer position was established (now called the Public Relations Officer) to represent EMWA to the public. In addition, to encourage EMWA members to volunteer, the subcommittee organisation was put on firm footing. The EMWA "members only" section of the website was introduced, as was the first 5-year strategic plan. EMWA also contributed to the update of the guidance for Good Publishing Practice during Julia's time in office.



**Julia Forjanic Klapproth**

### Helen Baldwin (2009)

Helen presided over EMWA relocating its base from Switzerland to the UK, and engaging a new company, MCI Group, to administer the Head Office. Helen introduced the first web-based conference survey, reduced EMWA's expenses by negotiating preferred hotel rates for conferences, introduced online downloading of workshop assignments from the website, established the Executive Committee (EC) role of conference manager, reduced the term of vice president to 1 year, and began establishing a social media presence for EMWA.

### Laurence Auffret (2010)

Laurence was behind the design and first implementation of the 5-year EMWA Strategic Plan. The strategic plan details the future development of EMWA, a format is still used today. Laurence also had the idea of creating a standard EMWA presentation accessible to any member to download and use to promote the organisation, describe the scope of our activities, its benefits, the conferences, and the value of EMWA membership. During her term, a searchable archive of *The Write Stuff* was set up on the EMWA website and was very active in encouraging and recruiting new volunteers. She also continued the "buddy system" to help first-time attendees get oriented during the conferences. Laurence remains an active workshop leader with a keen interest in online communication.

### Rita Wellens (2011)

Over the years changes came about in EMWA as a result of crises where major decision had to be made to ensure the smooth running of the organisation.

In May 2011, EMWA was forced to find a new management company. Kingston Smith Association Management was selected thanks to a lot of hard work by Rita and the rest of the EC. Over the years, we have been quite satisfied with the way they are running EMWA's Head Office. During the year, with a lot of hard work by former Editor-in-Chief, Elise Langdon-Neuner, we also switched from our original publication, *The Write Stuff*, to a new professionally published journal, *Medical Writing*.

### Susan Bhatti (2012)

Susan made further strides in improving EMWA. During Susan's term in office, starting in 2012, the first EMWA Spring conference Symposium was organised, the Geoff Hall Scholarship was established, and a merchant's bank account was set for EMWA members enabling them to pay conference fees via credit card. Together with Vice President Andrea Rossi, she broadened EMWA's contact with other professional organisations such as the



**Susan Bhatti**

International Society for Medical Publication Professionals (ISMPP) and the Institute of Clinical Research. Susan's other accomplishments included extending the fall conferences to enable delegates to take up to four workshops, and initiating webinars and online voting for Executive Committee candidates.

### Andrea Rossi (2013)

Andrea became President of EMWA at a time when EMWA was financially sound, which allowed the Executive Committee to introduce additional strategic improvements for the future of the organisation that we are still building upon today.



**Andrea Rossi**

During Andrea's tenure as President, EMWA's finances continued to grow, giving us added optimism for its future. The EC also initiated a new voting system to help increase participation, and sponsorship, members, and conference attendance continued to grow, allowing subscription fees to remain stable. At the conferences, a full-day symposium was added, with officials from the European Medicines Agency attending the first installation. Phil Leventhal took over as Editor-in-Chief and, with a new Editorial Board, added new enthusiasm to the journal. EMWA also created a Social Media group and began establishing a presence of social media, and EMWA's website ([www.emwa.org](http://www.emwa.org)) was re-designed and re-launched thanks to a lot of hard work by Webmaster Diarmuid De Faoite and Kingston-Smith.

### Julia Donnelly (2014)

As you can see, social media became increasingly important for communicating between our members and for promoting the organisation. This continued during the presidency of Julia Donnelly, who also represented and spread the word about EMWA to a larger international audience.



**Julia Donnelly**

### Sam Hamilton (2015–2016)

Sam's presidency can be characterised as a time when a number of new initiatives were started to add value for our more experienced members. Sam put in an enormous effort to initiate and guide the Core Reference document for clinical study reports, the Expert Seminar Series, and the Regulatory Public Disclosure Special Interest Group (SIG).



*Sam Hamilton*

### Alison Rapley (2017)

During Alison's time as President, the document repository for all executive committee documents was set up as well as the EMWA conference mini-site. A dedicated email system was established for EMWA, using Office 365. The webinar programme was expanded, a position statement was drafted together with AMWA and



*Alison Rapley*



*EMWA members kicking up their heels at the conference dinner during the Spring 2016 conference in Munich*

ISMPP on the role of professional medical writers, and a dedicated managing editor was hired for *Medical Writing*.

### Postscript

As you can see EMWA has gone through a lot of changes. Our organisation continues to evolve as medical writing becomes increasingly well known and as the demand for excellent medical communicators continues to rise.

### Reference

1. Hall G. The History of EMWA: Personal (and possibly unreliable) recollections. *The Write Stuff*. 2008;17(1):9–11.

**Abe Shevak**

[aspscientist@googlemail.com](mailto:aspscientist@googlemail.com)



*The 2017 Executive Committee*

# EMWA News

## SECTION EDITOR



**Evguenia Alechine**  
ealechine@epsilonsci.com

Today we are an organisation of over 1,000 members with meetings twice per year, more than 130 active workshops, full day symposia, and expert seminar sessions at conferences in the spring.

certainly pertains to EMWA as we celebrate our 25th year. The first EMWA meeting in 1992 had 32 participants with no workshops. Today we are an organisation of over 1,000 members with meetings twice per year, more than 130 active workshops, full day symposia, and expert seminar sessions at conferences in the spring. EMWA owes its success to the many people who stepped up and helped when they were needed and of course to all of you who value our organisation and what it has to offer.

EMWA celebrated its 25th anniversary in December, and, on that occasion, Abe Shevack, EMWA's President, posted an article on the website titled "Recollections and Accomplishments of Past EMWA Presidents", which is worth your time. The article covers the period from 2008 through 2017 when EMWA underwent many important changes. To access the article, click on the 25th anniversary banner on the website.

Also, we are looking to post some amusing photographs from past conferences on the website. If you have photos that you would like to share, please send them to [webmanager@emwa.org](mailto:webmanager@emwa.org).

This year, at the annual conference in Barcelona, the sixth EMWA symposium will focus on medical devices, the recent changes in European legislation, and opportunities for

The Greek philosopher Heraclitus has been credited with the idea that there is nothing permanent except change. This

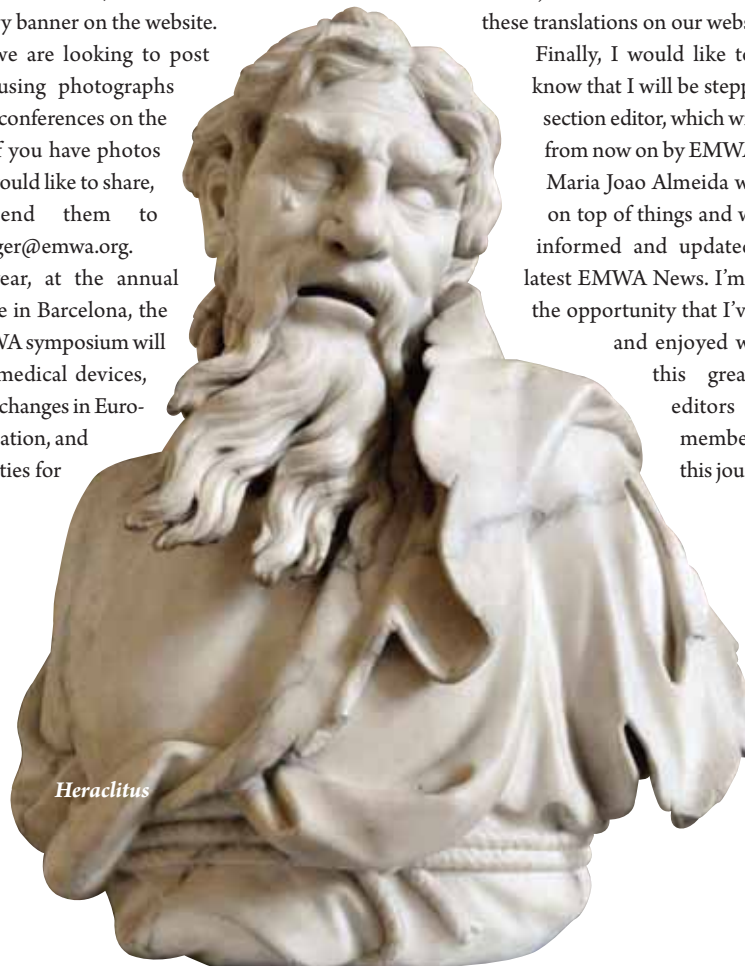
medical writers. The symposium is for regulatory writers and medical communicators alike and will provide the perspectives of different stakeholders, including legislators, notified bodies, medical device companies, patient representatives, and reimbursement professionals. The ESS will be focused on regulatory writing, orphan drugs and rare disorders, pharmacovigilance, and medical journalism.

Also, the Board of Editors in the Life Sciences exam will be offered once again in Barcelona on May 1, on the afternoon before the start of the conference (see [www.bels.org](http://www.bels.org) for more information about registration). Take advantage of this great opportunity to get certified as an editor in the life sciences.

The Joint Position Statement on the role of medical writers in preparing manuscripts for publication has now been translated into German, Italian, and French. The translations to Japanese and Chinese were recently posted on the ISMPP (International Society for Medical Publication Professionals) website. EMWA also has a link to these translations on our website.

Finally, I would like to let you all know that I will be stepping down as section editor, which will be covered from now on by EMWA's PR officer Maria Joao Almeida who is always on top of things and will keep you informed and updated about the latest EMWA News. I'm thankful for the opportunity that I've been given and enjoyed working with this great team of editors and EMWA members who make this journal possible.

The Greek philosopher Heraclitus has been credited with the idea that there is nothing permanent except change.



Heraclitus



# An introduction to vaccines and immunotherapies



**Jonathan M. Pitt and Julie Harriague**

4Clinics, Paris, France

## Correspondence to:

Jonathan M. Pitt  
4Clinics, 18-26 rue Goubet  
75019, Paris, France  
+33 (0)1 84 19 35 83  
jpitt@4clinics.com

## Abstract

Vaccines and immunotherapies are among the largest categories for pharmaceutical products, meaning that many medical writers will work in this field. For people new to this area, we describe the basics of how vaccines and immunotherapies work.

## Vaccines

Vaccines are among the greatest triumphs in public health of recent times and save 2 million to 3 million lives each year.<sup>1</sup> Smallpox, a once deadly disease, was confirmed to be eradicated in 1980 following a worldwide vaccination campaign.<sup>2</sup> Vaccines have also substantially reduced the incidence of several other major diseases in the past few decades, such as polio and measles. Today, licensed vaccines are available for preventing more than 30 different infectious diseases, several of which can be combined or administered at the same vaccination visit.<sup>1</sup>

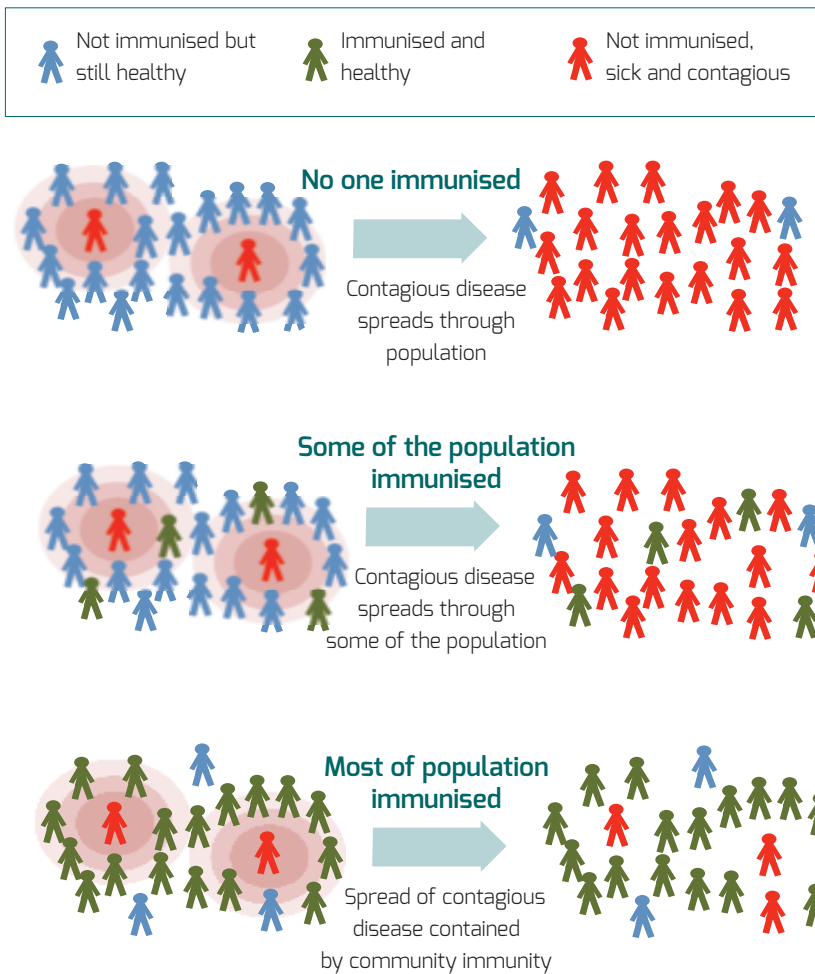
Because vaccines are given as preventive measures to large populations of healthy individuals, especially infants and children, a highly favourable benefit-risk profile is essential. When adverse events do occur, these are usually mild and transient and are typically centred at the injection site (e.g., injection site pain, redness, swelling). Mild and transient systemic reactions can also occur with some vaccines,

such as headache and fever.

Although they are usually considered for individual protection, vaccines can also protect unvaccinated people by reducing person-to-person transmission (Figure 1). This indirect protection, termed “community” or “herd” immunity, usually requires high vaccination coverage (75% to 95% of a target population) but can be essential for successful vaccination campaigns, such as for measles.<sup>3</sup> Similarly, vaccination of pregnant women can also protect infants in their first months of life due to cross-placental transfer of maternal antibodies. Maternal vaccination is currently used to protect mothers and infants against tetanus, influenza, and pertussis.<sup>4</sup>

## Immunotherapies

While new vaccines are being continually developed, researchers, clinicians, and pharmaceutical companies have become increasingly interested in immunotherapies. Immunotherapy



**Figure 1. Herd immunity**

When a critical portion of a community is immunised against a contagious disease, most of the community are protected against that disease. This is known as “community” or “herd” immunity. The top panel depicts a population in which no one is immunised and an outbreak occurs. In the middle panel, some of the population is immunised but not enough to confer community immunity. In the bottom panel, a critical portion of the population is immunised, which contains the spread of the disease and protects those not immunised. Adapted from Tkarcher – Own work, CC BY-SA4.0, <https://commons.wikimedia.org/w/index.php?curid=56760604>.

may be defined as the treatment of disease by modulating the immune response. By this definition, it could be argued that some vaccines are a form of immunotherapy, for example therapeutic vaccines.<sup>5</sup>

Many of the drugs approved in recent decades have been immunotherapies, and considerably more are advancing through pharma and biotech drug pipelines. Most immunotherapies are biological agents, for example cytokines, inhibitory or activating monoclonal antibodies, engineered lymphocytes, and allergens. Most notably, immunotherapies have shown unprecedented efficacy against several cancers, including melanoma and lymphoma, and are in clinical trials for many others.<sup>5</sup>

However, the same mechanisms of action that give immunotherapies their efficacy can also cause adverse events. Stimulating immune responses, as in the case of cancer immunotherapy, can result in various immune-related adverse events such as gastrointestinal, hepatic, and skin inflammation, which can range from mild to lethal.<sup>6</sup> Suppressive immunotherapies can also cause adverse events, such as increased susceptibility to infections.<sup>7</sup>

### How do vaccines and immunotherapies work?

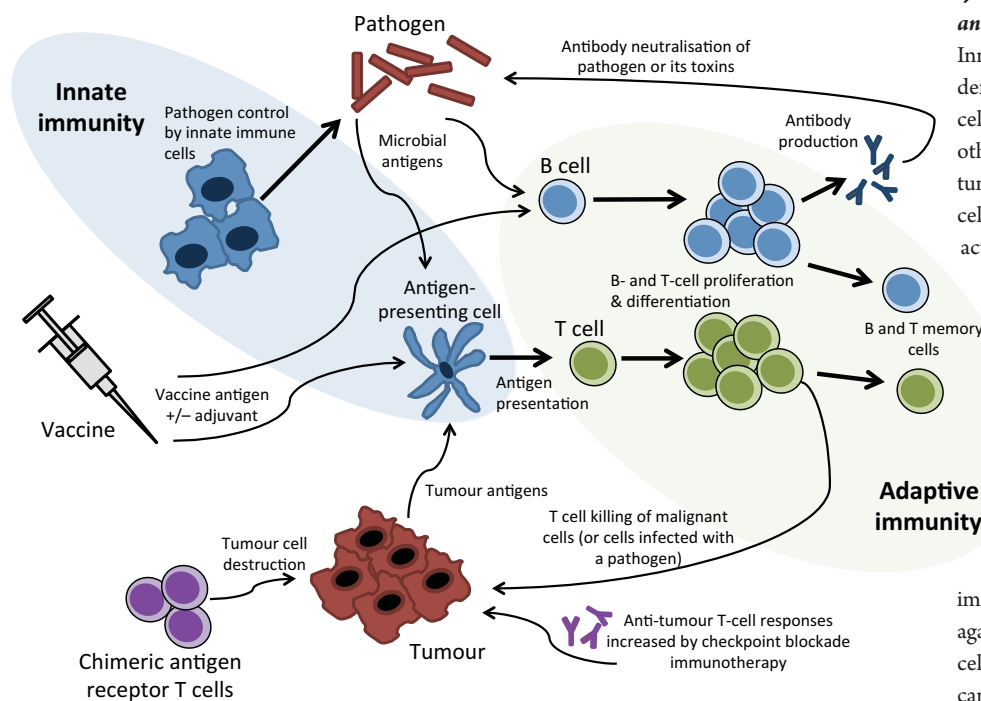
To understand how vaccines and immunotherapies work, one must first know the basics of how the immune system protects against infection and cancer. The vertebrate immune system can be divided into two categories of defence: innate immunity and adaptive immunity (Figure 2).<sup>8</sup> However, these distinctions are not mutually exclusive.

Innate immunity represents the first line of host defence against pathogenic micro-organisms. Innate immune cells (e.g., macrophages, neutrophils) recognise a limited set of danger signals and microbial molecular determinants shared by different pathogens. On recognising these threats, innate immune cells act within minutes by engulfing pathogens and inducing inflammation and further immune cell recruitment. Another important role of certain innate immune cells is antigen presentation and activation of adaptive immunity.

Adaptive immune cells, notably T and B lymphocytes, provide the second line of defence, generally at a later stage of infection. Unlike innate immunity, adaptive immunity is antigen-

specific (i.e., recognises a particular type of pathogen via a specific antigen) and capable of providing the immune “memory” that protects against re-infection with the same pathogen. Every encountered pathogen expresses or contains antigens, each one of which can activate a specific lymphocyte. When a T lymphocyte is activated by an antigen-presenting cell, it proliferates to form clone T cells that go on to recognise and eliminate infected (or malignant) host cells containing the specific antigen. Activated B lymphocytes similarly proliferate to give clones of B cells that differentiate into antibody-producing cells. The antibodies they produce recognise and neutralise pathogens or toxic products expressing the particular antigen. After eliminating the pathogen, the adaptive immune response regresses, but leaves memory lymphocytes that can quickly proliferate to attack or produce antibodies against the same pathogen, even decades later, if it is encountered again.

Vaccines act by initiating innate and adaptive immunity to produce long-term immunological memory against disease-causing pathogens. However, unlike a natural infection, vaccines do not cause the disease because they only contain



**Figure 2. The innate and adaptive immune system and points of interaction with vaccines and immunotherapies**

Innate immune cells form the first line of defence against many pathogens. Some innate cells can directly kill certain pathogens, while others take up antigens from pathogens, tumours, and vaccines and present these to T cells to activate adaptive immunity. Antigen-activated T cells proliferate and differentiate, and the resulting T cell clones go on to recognise and eliminate infected host cells or tumour cells expressing the specific antigen. Activated B cells similarly proliferate and differentiate to give clones of antibody-producing cells. Some T and B cells differentiate into memory cells that can quickly attack or produce antibodies if the same pathogen if it is encountered again. Some immunotherapies help adaptive immunity against tumours: chimeric antigen receptor T cells are engineered to recognise and eradicate cancer cells expressing certain tumour antigens; checkpoint blockade immunotherapies consist of antibodies that block molecular regulators of T cell activation, resulting in enhanced anti-tumour immune responses.

inactivated or attenuated micro-organisms, or selected antigenic fragments from pathogens (“subunit vaccines”) (Table 1).<sup>9</sup> Vaccine development has made significant progress from the early days of empirical design to today’s rational vaccine designs based on the biology of the targeted infection and the disease to be prevented.

Vaccine “adjuvants” – substances that enhance and modulate the immunogenicity of the vaccine’s antigens – can be just as important in vaccine design as the vaccine antigen itself. Adjuvants are used to activate innate immunity, improve memory responses, and broaden or extend innate and adaptive immune responses. This can help to reduce the amount of antigen per dose or the number of doses needed for a given vaccine. Subunit vaccines usually require adjuvants because they contain fewer antigens and may lack some molecular components of whole pathogens that trigger innate immune cells.

Immunotherapies, on the other hand, may be designed to amplify an immune response or to

**Vaccines act by initiating innate and adaptive immunity to produce long-term immunological memory against disease-causing pathogens.**

reduce it. This can be achieved by targeting various stages in innate and adaptive immunity, for example by neutralising specific inflammatory or immunosuppressive cytokines, or by inhibiting regulatory molecules involved in antigen presentation to T lymphocytes. Cancer immunotherapy, one of the most active areas of R&D today, usually involves reactivating immune responses against cancer cell antigens, which

have been switched off by the immunosuppressive environment within tumours. In contrast, immunotherapies for autoimmune diseases are usually designed to suppress immune-mediated destruction of host tissues.

**Conclusion**

Our improved understanding of the immune system and its interactions with pathogens, allergens, and cancer cells has heralded new vaccine and immunotherapeutic designs along with unprecedented clinical successes. Vaccines and cancer immunotherapies were among the largest categories for pharmaceutical R&D

products in 2017.<sup>10</sup> Accordingly, understanding the basic concepts of these agents, and their benefits and risks, is crucial for medical writers who might be involved in such projects.

**Conflicts of interest**

The authors declare no conflicts of interest related to this article.



Table 1. Examples of different vaccines and immunotherapies

Type	Subtype	Explanation	Examples
Vaccines	Inactivated	Infectious agent (e.g. virus) “killed” by chemicals or heat	Whole-cell pertussis, rabies, and injected polio vaccines
	Live attenuated	Weakened version of the infectious agent (e.g. virus)	Mumps-measles-rubella (MMR), oral polio, and bacille Calmette-Guérin (BCG) vaccines
	Subunit	Only antigenic region of the infectious agent	Tetanus toxoid, influenza, and pneumococcal vaccines
Immunotherapies	Monoclonal antibodies	These neutralise or block certain proteins or may deliver radioisotope or chemicals to mediate targeted cell killing	Anti-tumour necrosis factor (TNF) antibody for treating rheumatoid arthritis, immune checkpoint inhibitors for boosting T-cell responses against tumours
	Cell-based	Injection of modified activated immune cells that fight threats (e.g. malignant cells)	Chimeric antigen receptor (CAR) T cells that eliminate leukemic cells
	Suppression	Suppress the immune system or induce tolerance	Allergen desensitisation, immunosuppressive drugs
	Cytokines	Immune signalling molecules that modulate immune responses	Interleukin-2, interferon- $\alpha$



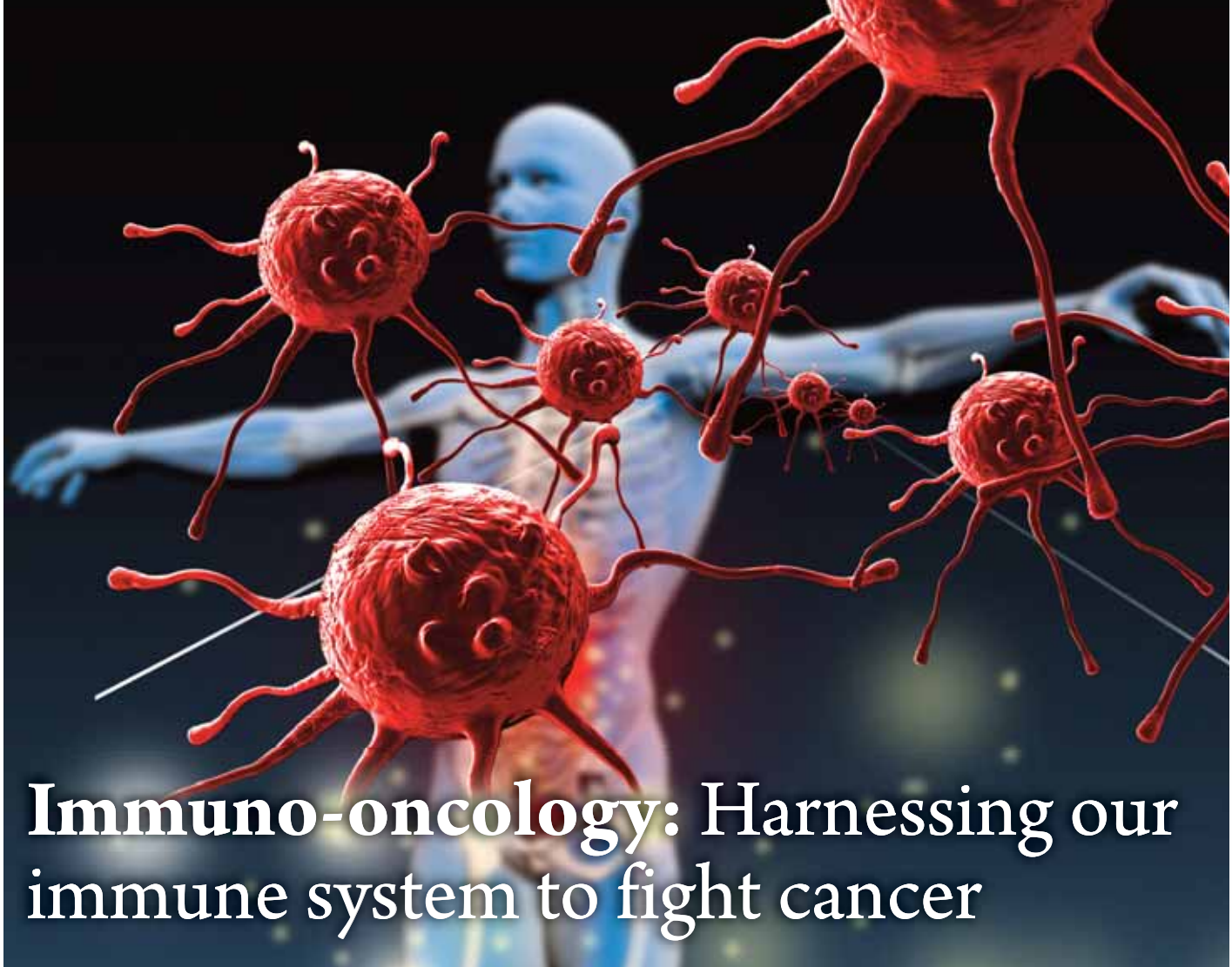
## References

- Delany I, Rappuoli R, De Gregorio E. Vaccines for the 21st century. *EMBO Mol Med.* 2014;6:708–20.
- Henderson DA. The eradication of smallpox—an overview of the past, present, and future. *Vaccine.* 2011;29 Suppl 4:D7–9.
- Scarborough Lefebvre CD, Terlinden A, Standaert B. Dissecting the indirect effects caused by vaccines into the basic elements. *Hum Vaccin Immunother.* 2015;11:2142–57.
- Swamy GK, Heine RP. Vaccinations for pregnant women. *Obstet Gynecol.* 2015;125:212–26.
- Dalgleish AG. Vaccines versus immunotherapy: overview of approaches in deciding between options. *Hum Vaccin Immunother.* 2014;10:3369–74.
- Cousin S, Seneschal J, Italiano A. Toxicity profiles of immunotherapy. *Pharmacol Ther.* 2018;181:91–100.
- Minozzi S, Bonovas S, Lytras T, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf.* 2016;15:11–34.
- Moser M, Leo O. Key concepts in immunology. *Vaccine.* 2010;28 Suppl 3:C2–13.
- Vetter V, Denizer G, Friedland LR, Krishnan J, Shapiro M. Understanding modern-day vaccines: what you need to know. *Ann Med.* 2017:1–11.
- Pharma R&D annual review 2017. *Pharmaprojects Pharma Intelligence.* Informa. 2017 [cited 2018 Feb 2]. Available from: <http://pharma.intelligence.informa.com/pharmaproj-rndannualreview-Social-Report?elqTrack=true>.

## Author information

**Jonathan M. Pitt, PhD**, is a medical writer for 4Clinics, France, and has over 10 years of experience in onco-immunology, infection and immunity, and vaccines. Before entering medical writing, he held several research positions in academia and the pharmaceutical industry in the UK and France.

**Julie Harriague, PhD**, has been working as a scientific writer at 4Clinics, France, since 2007. She specialises in writing publications in the areas of vaccines and infectious diseases.



# Immuno-oncology: Harnessing our immune system to fight cancer

Anne Rascle<sup>1</sup> and Trevor Stanbury<sup>2</sup>

1 Lophius Biosciences, Regensburg, Germany  
2 UNICANCER, Paris

## Correspondence to:

Anne Rascle  
Lophius Biosciences  
Am BioPark 13  
93053 Regensburg, Germany  
+49 (0) 941 630 919 787  
anne.rascle@ur.de

## Introduction

Cancer immunotherapy began in the late 19th century when the New York surgeon and cancer researcher William Coley noted cases of spontaneous remission of sarcoma in patients who had developed acute *Streptococcus pyogenes* infections.<sup>1,2</sup> Coley hypothesised that *Streptococcus* stimulating the immune system with a bacterial infection might be associated with a bystander anti-tumoural activity that would result in tumour regression. So, in 1891 Coley began treating mainly inoperable sarcoma

## Abstract

The history of immunotherapy to treat cancer began in 1891 when the American surgeon William Coley performed intra-tumoural injections with inactivated bacteria in patients with advanced sarcoma, in an attempt to stimulate anti-tumour immunity. Modern immunotherapy gradually made its way over the last 50 years, as a better understanding of anti-cancer immunity has been gained. Immunotherapeutic agents target three essential steps in the immune response to tumour-associated antigens, namely antigen presentation, effector T-cell response, and inhibition of tumour-driven immunosuppression. Conventional chemotherapy and immunotherapy agents differ in their mode of action, predicted endpoints, and toxicities. The development and approval of immunotherapy drugs has therefore challenged our traditional view of conducting clinical trials. Many challenges with great promises still lie ahead, including combination therapies and individualised therapy based on patients' predicted responses to treatments.

patients with intra-tumoural injections of initially live and then inactivated *Streptococcus pyogenes* and *Serratia marcescens* (so-called Coley's toxins).<sup>2,3</sup> However Coley's approach fell into disuse, hampered by a cure rate of 10%, an absence of standardised toxin manufacturing, the lack of prospective clinical trials to evaluate the safety and efficacy of this treatment, and the arrival of modern cancer treatments (radiation therapy and chemotherapy).<sup>2,4</sup> One exception is the current use of intravesical injection of live bacillus Calmette-Guérin (BCG) as an efficient approach to treat superficial bladder cancer.<sup>5</sup>

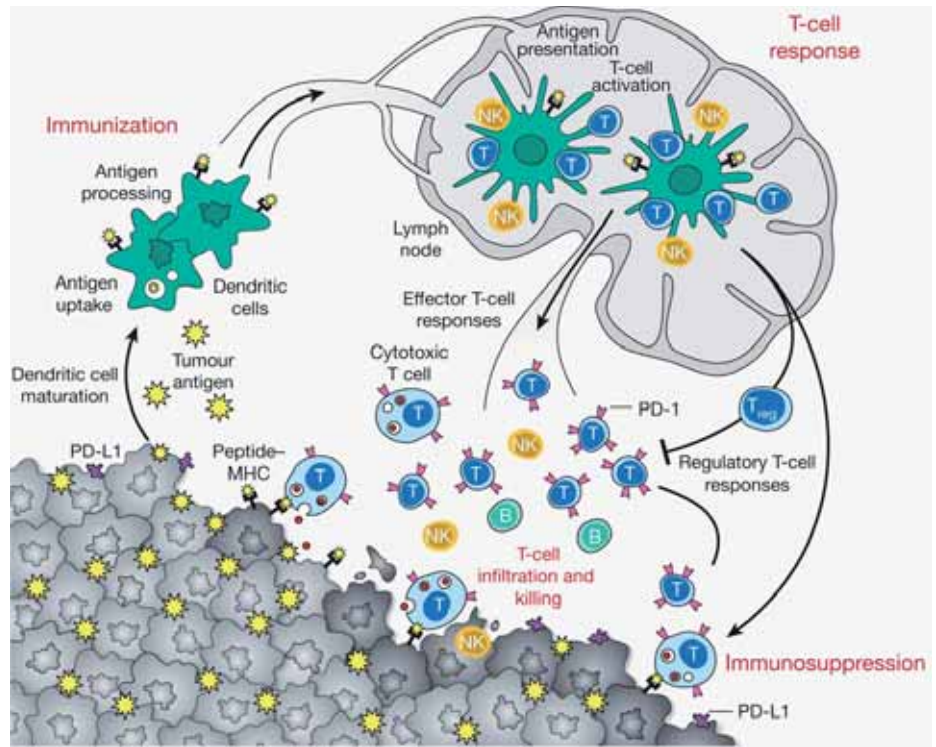
Since Coley's procedure, the concept of immune surveillance has emerged, and it is now well established that the immune system recognises and eliminates cancer cells. A failure in immune surveillance (or immune escape) is associated with cancer initiation and progression.<sup>6,7</sup> Immuno-oncology thus originated as an approach to stimulate or restore the patient's immune response to cancer. Before reviewing the state-of-the-art and future of immunotherapies, it is necessary to describe the processes underlying a protective immunity to cancer and the challenges we face.

## Generation and regulation of anti-cancer immunity

Our immune response to tumours follows three main successive steps (Figure 1).<sup>8,9</sup> The initial step, called tumour recognition, occurs when tumour-associated proteins (or antigens) released by dead or dying tumour cells are captured by specific immune cells, mainly dendritic cells. These cells process the antigens and present them on their surface. This is why these dendritic cells are also known as antigen-presenting cells.<sup>10</sup> When dendritic cells process and present tumour-associated antigens, they also need to receive an activation (or maturation) signal, which can occur by a number of different immune-stimulating pathways. Typical immune-stimulating signals, sometimes referred to as “endogenous” adjuvants (in contrast to “exogenous”, therapeutically administered adjuvants; see below), are pro-inflammatory cytokines, co-stimulatory CD40/CD40L proteins, factors released by dying tumour cells such as adenosine triphosphate (ATP) or high-mobility group box 1 protein (HMGB1), or toll-like receptor (TLR) ligands.<sup>10</sup>

**A failure in immune surveillance is associated with cancer initiation and progression. Immuno-oncology thus originated as an approach to stimulate or restore the patient's immune response to cancer.**

The second step involves generating an immune response to the tumour. This occurs when the antigen-presenting dendritic cells travel to the lymph nodes where they elicit an immune response called an antigen-specific T-cell response.<sup>11</sup> If there isn't a co-stimulatory maturation signal, “immature” dendritic cells suppress the immune response to the tumours by promoting the formation of immunosuppressive regulatory T-Cell ( $T_{reg}$ ), or by inducing T-cell depletion or anergy (the absence of a response to an antigen).<sup>12</sup> This phenomenon of immune suppression is also known as immune tolerance. If the antigen-presenting cell received a co-stimulatory maturation signal, these “matured” dendritic cells provoke or stimulate a T-cell response (mainly effector cytotoxic T cells). This T-cell response is also dependant on specific interactions between dendritic cells and T-cell co-stimulatory molecules.<sup>13,14</sup> For instance, interaction of



**Figure 1. Generation and regulation of anti-tumour immunity**

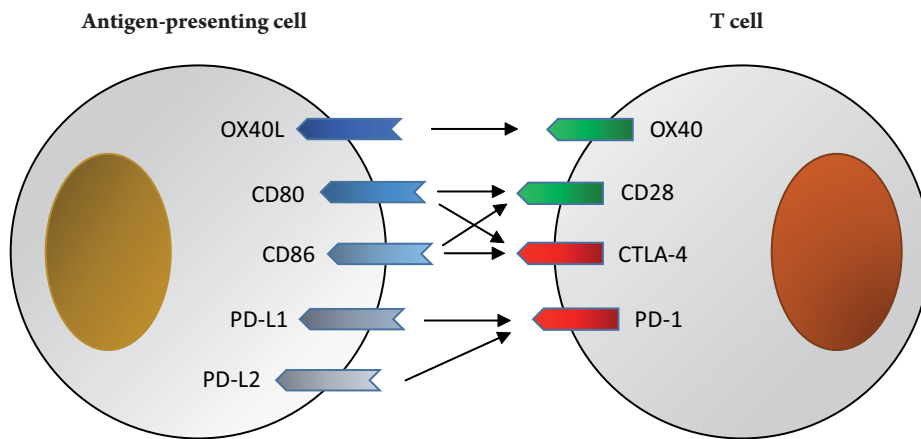
Anti-tumour immunity is initiated with the capture of tumour-associated antigens (delivered by dead or dying tumour cells) by dendritic cells. Tumour antigens are processed and presented on major histocompatibility complex (MHC) molecules to naïve T cells in the lymph node (immunisation). In the presence of a maturation signal (“adjuvant”), and depending on their interaction with T-cell co-stimulatory molecules, dendritic cells elicit an anticancer effector T-cell response (cytotoxic T cell priming and activation). These effector cytotoxic T-cells traffic to and infiltrate the tumour bed, together with B and NK cells, causing the killing of antigen-specific tumour cells. In the absence of a maturation signal in the lymph node, however, dendritic cells induce tolerance by promoting regulatory T-cell ( $T_{reg}$ ) responses and T-cell anergy.  $T_{reg}$  further infiltrate and accumulate into the tumour bed, contributing to the immunosuppressive environment established by tumour cells and other infiltrating myeloid-derived suppressor cells. Notably, tumour cells overexpress the PD-L1 molecule which engages the PD-1 receptor on effector T cells, causing their exhaustion. Immunotherapeutic interventions target the three major steps of anticancer immunity: immunisation, generation of a protective T cell response, and overcoming immunosuppression imposed by the tumour microenvironment. Figure reprinted by permission from Macmillan Publishers Ltd: Nature (volume 480, issue 7378, page 481), copyright (2011).<sup>8</sup>

CD80/CD86 (on dendritic cells) with CD28 (on T cells) or OX40L with OX40 will stimulate, while interaction of CD80/CD86 with CTLA-4 or PD-L1/PD-L2 with PD-1 will suppress T-cell responses (Figure 2). T-cell priming and activation is therefore a critical stage that determines the nature of the immune response.

In the third and last step, cytotoxic T cells exit the lymph node together with other tumour antigen-specific lymphocytes (B cells, natural killer [NK] cells, and natural killer T [NKT] cells), reach the bloodstream, and head toward the tumour site.<sup>8,9</sup> There, they enter the tumour bed where cytotoxic T cells recognise and then kill the cancer cells (Figure 1). In turn, these dead

and dying cells provide a novel source of tumour antigens (also called neo-antigens), which initiate a new immunity cycle.<sup>8,9</sup>

However, killing cancer cells is not that simple. Within the tumour site, cytotoxic T cells then face an immunosuppressive environment. Tumour cells, as well as other cells infiltrating the tumour tissue, so-called myeloid-derived suppressor cells (MDSCs), use a variety of strategies to suppress the function of cytotoxic T cells. For instance, tumour cells release T-cell suppressor molecules such as prostaglandin E2 ( $PGE_2$ ) and indoleamine 2,3-dioxygenase (IDO),<sup>15</sup> while MDSCs produce inhibitory molecules such as arginase and nitric oxide



**Figure 2. Examples of activating and inhibitory signaling between an antigen-presenting cell and a T cell**

The interaction of activating (green) or of inhibitory (red) co-stimulatory molecules on the T cell surface with their respective receptor on the antigen-presenting cell (dendritic cell) contributes to either immune activation and the development of anti-tumour immunity or to immune suppression and the development of immune tolerance, respectively. Of note, tumour cells frequently express programmed cell death ligand (PD-L1/PD-L2) molecules on their surface, which engage PD-1 receptors on cytotoxic T cells, suppressing their anti-tumour activity. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1/PD-L2, programmed cell death protein ligands 1 and 2; OX40L, OX40 ligand; CD, cluster of differentiation (CD28, CD80, and CD86 proteins).

synthase.<sup>16</sup> More importantly, tumour cells express programmed cell death protein ligand (PD-L1/PD-L2) molecules on their surface, which engage PD-1 receptors on the cytotoxic T cells, causing their anergy.<sup>17</sup> Reduced oxygenation within the tumour tissue (intratumoural hypoxia), a common feature of rapidly growing tumours, results in the release of immunosuppressive molecules (e.g., vascular endothelial growth factor A [VEGFA], adenosine, CCL28) that also contribute to the local immunosuppression.<sup>18–21</sup> Alternatively, tumours have also developed mechanisms to interfere with antigen presentation,<sup>8,9</sup> thereby suppressing the initial step of the immune response (Figure 1). All these tumour-driven immunosuppressive mechanisms make it challenging for cytotoxic T cells to efficiently target and kill cancer cells.

Based on our current knowledge of anticancer immunity, described above, immunotherapies can intervene at three critical stages by:

1. stimulating antigen processing and presentation by dendritic cells
2. stimulating the T-cell responses in lymph nodes
3. overcoming the immunosuppressive mechanisms within the tumour micro-environment

Different immunotherapeutic interventions have been proposed at each of these stages. At the

first stage, an intervention may be a therapeutic cancer vaccine that introduces tumour-specific antigens from outside of the body (exogenously) to stimulate the T-cell response. At stage 2, an intervention may be delivering adjuvants exogenously that initiate dendritic cell maturation (such as TLR ligands, CD40 antibodies that activate receptors on the dendritic cell, or even by provoking tumour cell lysis and the release of the adjuvant molecules ATP or HMGB1). At stage 3, antagonizing immunosuppression at the tumour site can be attempted by blocking the PD-L1/PD-1 interaction between the tumour cells and the cytotoxic T cells, by counteracting the effect of immunosuppressive molecules (e.g., IDO, adenosine), or by enhancing the recognition of cancer cells by cytotoxic T cells (Figure 3).

### Immunotherapies

The aim of anticancer immunotherapy is to initiate, stimulate, or restore anti-tumour immunity without disrupting the self-tolerance mechanisms, which would result in pathological autoimmune inflammatory responses. The better understanding of anti-

cancer immunity acquired over the past 5 decades has allowed a more educated design of immunotherapies, and their use as monotherapy or, more recently, in combination with other treatment regimens (chemotherapy, radiotherapy, and surgery).<sup>4,8</sup>

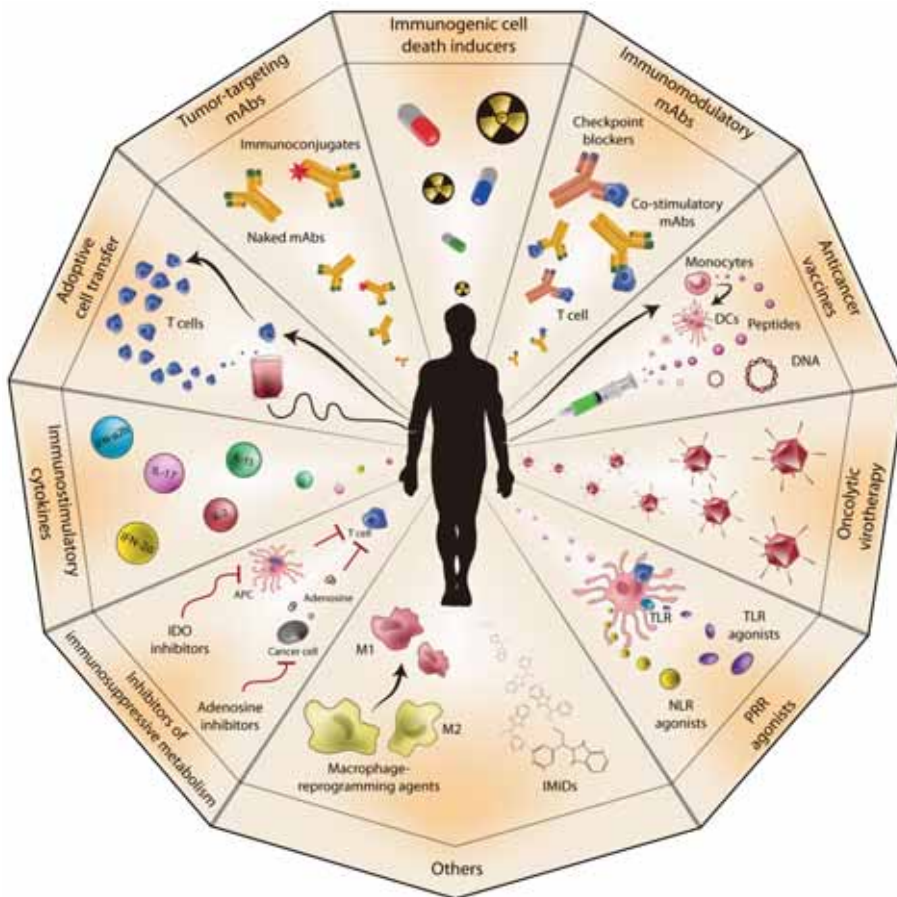
In the past, cancer immunotherapies were classified as being either passive or active. Passive immunotherapies were usually defined as those stimulating a patient’s own immune response whereas active immunotherapies were those inducing a *de novo* immune response to directly attack tumour cells. However, this definition is often misused in the literature and not always relevant;<sup>22–24</sup> the terms of passive and active therapies can be misleading and should probably be revised. Here, immunotherapies are described according to their ability to either modulate an existing immune response or to provoke a *de novo* or replace a missing immune response (Figure 3 overleaf).

Immunotherapies that modulate the immune response include immunomodulatory monoclonal antibodies (co-stimulatory or blocking antibodies), immunostimulatory cytokines (e.g. interleukin [IL]-2), and small molecules (e.g., inhibitors of immunosuppressive metabolism such as IDO or adenosine inhibitors), which boost the immune response or block immunosuppressive T cell functions (Figure 3).<sup>4,8,9,22,23</sup>

Anti-PD-1 (nivolumab, pembrolizumab) and anti-CTLA-4 (ipilimumab) blocking antibodies, also known as checkpoint inhibitors or checkpoint blockers (Figure 3), are FDA-approved immunotherapeutic drugs. They represent a major breakthrough in immuno-oncology. These checkpoint inhibitors can restore anti-tumour T-cell function and showed clinical benefit to some cancer patients (see below).<sup>4,8,9,22,23</sup>

Immunotherapies that provoke a *de novo* or replace a missing immune response include cell therapy (known as adoptive cell transfer), anticancer vaccines, oncolytic viruses, and bispecific T-cell engagers (BiTEs).<sup>4,8,9,22,23</sup> Conventional adoptive cell therapy consists of isolating tumour-infiltrating T cells from a cancer patient; once isolated, the T cells are expanded *in vitro*, and then reintroduced into the patient, providing

The aim of anticancer immunotherapy is to initiate, stimulate, or restore anti-tumour immunity, without disrupting the self-tolerance mechanisms, which would result in pathological autoimmune inflammatory responses.



**Figure 3. Anticancer immunotherapy**

Anti-cancer immunotherapeutics include tumour-targeting (e.g. BiTEs, anti-VEGFA inhibitor) and immunomodulatory (e.g. anti-PD-1 and anti-CTLA-4 immune checkpoint inhibitors) monoclonal antibodies (mAbs); dendritic cell (DC)-, peptide- and DNA-based anticancer vaccines; oncolytic viruses; pattern recognition receptor (PRR) agonists (e.g. TLR agonists); immunostimulatory cytokines (e.g. IL-2); immunogenic cell death inducers (radiation therapy, chemotherapy); inhibitors of immunosuppressive metabolism (e.g. IDO or adenosine inhibitors); and adoptive cell transfer. APC, antigen-presenting cell; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; IMiD, immunomodulatory drug; NLR, NOD-like receptor; TLR, Toll-like receptor. Figure reprinted with permission of *Oncotarget*, under the terms of the Creative Commons Attribution License.<sup>23</sup>

immune protective cells. Recently, two very promising cell therapy methods (so-called T cell receptor [TCR] and chimeric antigen receptor [CAR]), which are under development and clinical evaluation, have been described. These promising therapies are based on isolating T cells from a patient's blood; these isolated T cells are then manipulated *in vitro* to redirect their specificity toward tumour-specific antigens, before being reintroduced into the patient. Anticancer vaccines (e.g., dendritic cell-, whole-tumour-, DNA- or peptide-based) deliver tumour-specific antigens to initiate an immune response. Oncolytic viruses (OVs) selectively infect and kill tumour cells. Bispecific T-cell engagers (BiTEs) are antibody-based recombinant molecules that force the recognition of

tumour-associated antigens on tumour cells by cytotoxic T cells and the subsequent activation of anti-tumour cytotoxic activity (Figure 3).<sup>4,8,9,22,23</sup>

### Clinical study design

Oncology drug development in humans, before marketing approval, has followed a traditional sequence of trials. Phase I trials identify the maximum tolerated dose (MTD) and evaluate the toxicity, pharmacodynamics, and pharmacokinetics of the new drug. In oncology, for ethical reasons, patients and not healthy volunteers are enrolled in phase I trials. Once the MTD has been identified, the recommended phase II dose is established and phase II trials are initiated. Phase II trials assess drug activity and tolerance

in usually a few hundred patients. If the new drug shows sufficient activity and reasonable tolerance, phase III studies are initiated. Phase III trials compare the drug to existing treatments or placebo in a larger population.<sup>25</sup>

The recent development of cancer immunotherapies has substantially changed the traditional drug development methodology used in oncology.<sup>26</sup> The development and approval of the immunotherapy pembrolizumab is a good example of how this process has accelerated in recent years.<sup>27</sup> Pembrolizumab is a monoclonal antibody that binds to programmed cell death protein 1 (PD-1) on cytotoxic T cells. This binding prevents programmed cell death ligands 1 and 2 (PD-L1 and PD-L2) proteins, on tumour cells, from interacting with PD-1 that deactivates the cytotoxic T cells and diminishes the immune response. In 2011, a first-in-human phase Ib clinical trial was initiated to identify the recommended phase II dose for patients with advanced solid tumour cancers. However, pembrolizumab seemed to have a high level of activity and so additional patients were enrolled for two other tumour cohorts – melanoma and non-small cell lung cancer (NSCLC). Since oncology trials enrol patients rather than healthy individuals in phase I trials, drug activity can be explored at this early stage. It became increasingly evident that pembrolizumab had superior activity as more patients were assessed, and so additional patients were included in other tumour cohorts. Overall, more than 1,200 patients were recruited in this open-label phase Ib trial. In September 2014, pembrolizumab obtained marketing approval for the treatment of metastatic or inoperable melanoma via an accelerated process based on the phase Ib results. Then in October 2015, this approval was extended to the treatment of those NSCLC patients that express the programmed cell death ligand 1 (PD-L1) protein. This seamless drug development of pembrolizumab was substantially quicker than the traditional sequence of trials. Although the development time is remarkably shorter, clinical study design with immunotherapies are challenging in other respects. As the tumour response to immunotherapy agents depends on the individual patient's immune function, this response does not follow the same pattern as that observed upon administration of traditional chemotherapy agents. Cytotoxic chemotherapy agents directly attack and kill cancer cells and thus an increase



in dose usually increases the efficacy. However, immune-targeting agents either stimulate immune cells or alternatively prevent cancer cells from deactivating the immune response. With this mechanism of action, dose does not always correlate with efficacy. Furthermore, the anti-tumour response to immunotherapies is often delayed compared to that of conventional cytotoxic therapies. As an example, melanoma patients treated with ipilimumab continued to respond beyond 24 weeks of treatment.<sup>28</sup> In contrast, the tumour response to chemotherapy usually occurs early during treatment.

The use of a traditional phase I study design to evaluate immunotherapies generates issues. First, in many phase I studies, the MTD of the immunotherapeutic agent was never reached. Thus, identifying the minimum effective dose, the maximum effective dose, and the maximum administered dose in phase I immunotherapy studies is more relevant than the MTD for estimating the recommended phase II dose.<sup>29</sup> Furthermore, the sample size of expansion cohorts in phase I immunotherapy studies are often not justified, despite having efficacy as exploratory objectives. When designing these trials, it is important to ensure that they are designed with the same statistical rigour as traditional phase II studies – allowing for false-positive and false-negative results and with interim futility stopping rules to prevent unethical treatment of patients.

At present, the Response Criteria In Solid Tumours (RECIST) classification is used to assess tumour response required to evaluate new treatments in oncology. However, with immunotherapies there is often an initial tumour flaring, an increase in tumour size possibly in response to inflammation, before eventual shrinkage. Using RECIST v1.1, an increase of at least 20% in the sum of the tumour lesion diameters would be classified as disease progression.<sup>30,31</sup> With treatments other than immunotherapies, this would result in a modification of treatment strategy. However, in the case of immunotherapies, this type of pseudo-progression may be a clear indication of a treatment response. Thus, RECIST, which assesses tumour response for

**As the tumour response to immunotherapy agents depends on the individual patient's immune function, this response does not follow the same pattern as that observed upon administration of traditional chemotherapy agents.**

outcomes such as progression-free survival (PFS), objective response rate (ORR) etc., needs to be adapted for immunotherapy trials. There have been a number of attempts to establish new classifications, e.g., iRECIST,<sup>32,33</sup> irRECIST,<sup>32,33</sup> and immune-related response criteria (irRC),<sup>34,35</sup> but these need validation and consensus.

Currently, most immunotherapy trials continue to use the RECIST classification to evaluate the tumour response for the primary endpoints (such as PFS, ORR). These traditional endpoints are considered acceptable for regulatory approval. In addition, some of these endpoints have been correlated with overall survival and considered as surrogate endpoints. However, to investigate immunotherapy-specific endpoints, such as immune-related PFS (irPFS) assessed by immunotherapy-specific classification (such as iRECIST, irRECIST, and irRC), these endpoints are often included as secondary endpoints. In addition, a central review of the imagery used to assess response is also often included. The aim is now to evaluate these new classifications for assessment of tumour response, as well as to validate these endpoints as surrogate endpoints for overall survival.

As with efficacy, the toxicity observed with immunotherapies does not follow the same pattern as that observed with traditional chemotherapy agents. Furthermore, immunotherapies have different toxicity profiles compared to cytotoxic agents. The toxicity profile depends on the immunotherapy agent, its mode of action, and the type of tumour that it targets.<sup>36</sup> The toxicities observed can broadly be divided into infusion reactions and immune-related adverse events (irAEs).<sup>37</sup> Infusional reactions,

**Our increase in knowledge of how the immune system responds to cancer and the development of immunotherapies that target these different stages have introduced new weapons in the arsenal to fight cancer. This development has also challenged the traditional way to develop and approve new drugs.**

allergic or non-allergic, are immune reactions that most frequently occur during the first administration of treatment.<sup>38,39</sup> Immunotherapies in general have a low incidence of infusion reactions. However, some immunotherapies have a non-negligible incidence of non-allergic reactions resulting from cytokine release. The release of cytokines causes a variety of symptoms, including fever, nausea, chills, hypotension, tachycardia, and fatigue. In terms of irAEs, the most frequently affected organs are the skin, colon, endocrine organs, liver, and lungs. Accordingly, the most common irAEs are diarrhoea, rashes, and fatigue.<sup>40</sup> In contrast to chemotherapies, the onset of irAEs is often delayed, some beginning as long as 1 year after treatment. Overall, immunotherapeutics are well tolerated but severe and life-threatening toxicities do occur. Clinical trial design should allow for the long-term collection of toxicity data and the possible relatedness to the immunotherapy. This is achievable in most cancer studies because extended patients' follow-up is usually incorporated to evaluate the overall survival benefit.

Patient selection is vital in immunotherapy studies. Despite the high activity of immunotherapies, like pembrolizumab and nivolumab, in treating certain cancers, only a minority of patients have long lasting remissions. Considering the toxicity profile, careful identification and selection of patients expected to benefit from immunotherapies has become essential. Patients with a pre-existing immune response and more inflamed tumours tend to respond better.<sup>41</sup>

The fact that patients with a pre-existing immune response tend to respond better to immunotherapies also provides a rationale for combining immunotherapies with other more classical therapies, including chemotherapies, radiotherapies etc. These classical therapies kill tumour cells liberating antigens that prime the immune system. In addition, radiotherapy induces an abscopal effect, the occurrence of an immune response outside of the irradiated field. Furthermore, combining immunotherapeutic agents targeting distinct steps of the immune response and at different time points might also prove to be beneficial.<sup>4,8</sup>

In summary, immuno-oncology is only in its infancy. Our increase in knowledge of how the immune system responds to cancer and the development of immunotherapies

that target these different stages have introduced new weapons in the arsenal to fight cancer. This development has also challenged the traditional way to develop and approve new drugs. Despite the proven efficacy of immunotherapies, these treatments are only effective for certain patients. There remain a number of important issues that need to be addressed, including: Which patients will benefit most from treatment and how should we combine immunotherapeutics with traditional therapies?

### Disclaimers

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

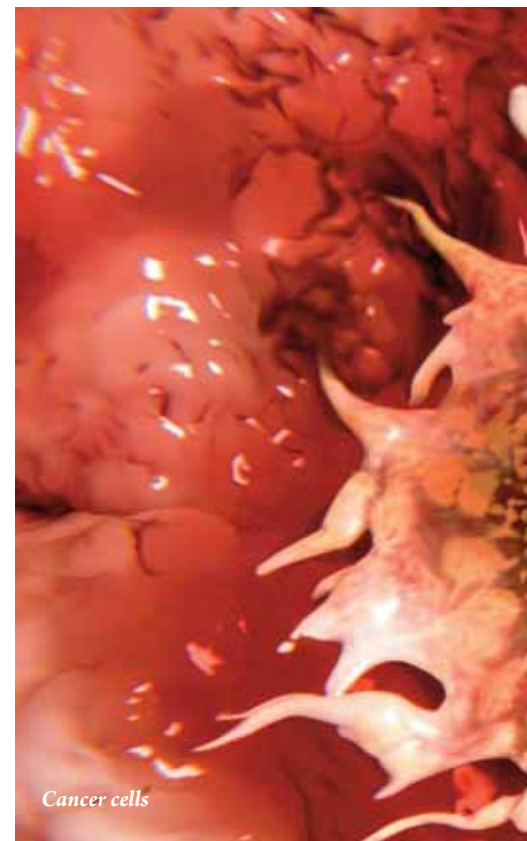
### Conflicts of interest

The authors declare no conflicts of interest related to this article.

### Author information

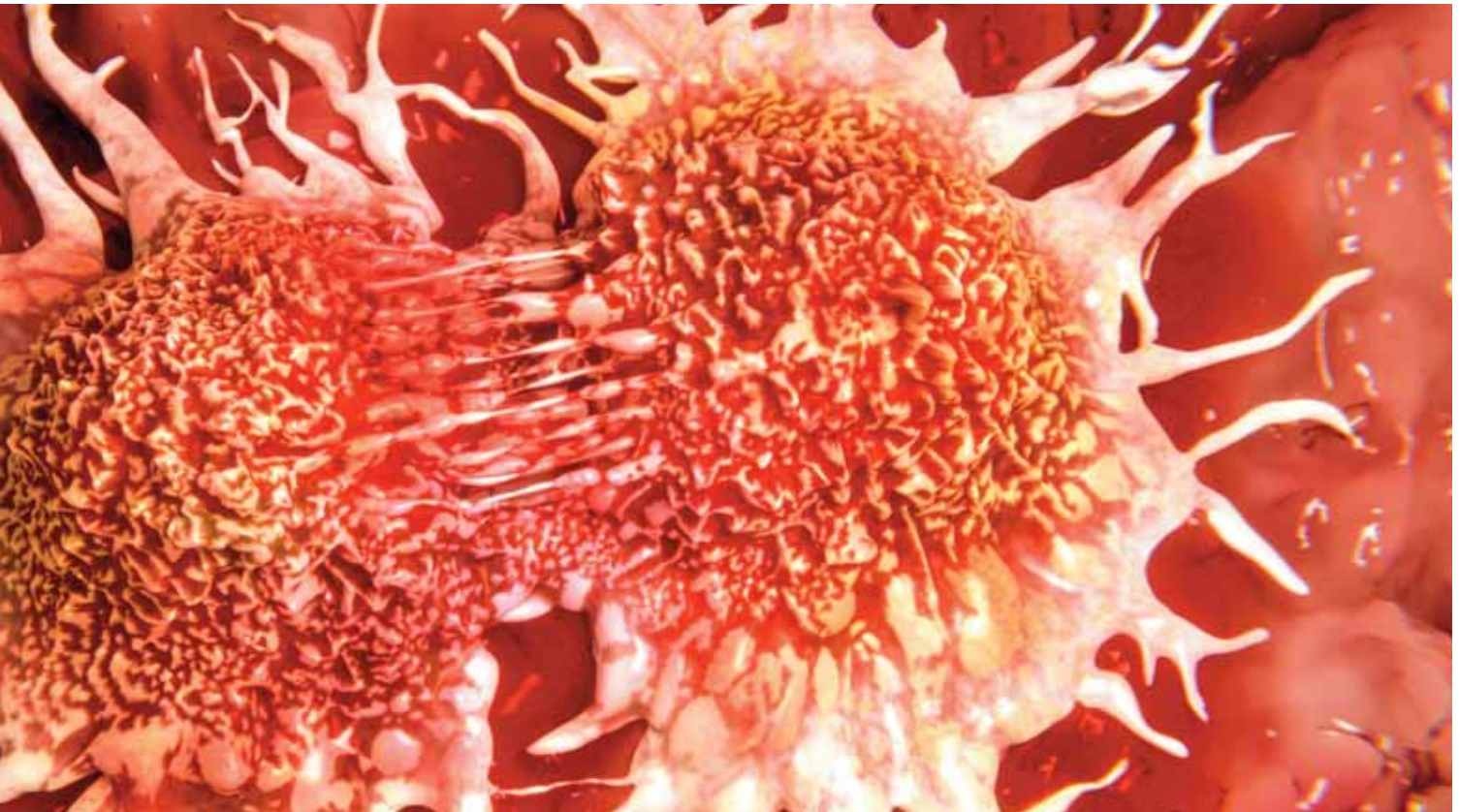
**Anne Rascle**, PhD, is a medical writer, specialising in publication writing and medical communication. She has been head of Scientific Affairs at Lophius Biosciences since 2016. She has 25 years' experience as an academic researcher in oncology and immunology in France, the United States, and Germany. She also teaches medical communication at the University of Regensburg.

**Trevor Stanbury**, PhD, is a medical writer at UNICANCER, based in Paris, specialising in writing for oncology clinical studies, including protocols, clinical study reports, and publications. He has a background in organic chemistry but for the last 11 years has been working in clinical studies. The last 5 years, he has worked specifically in oncology.



### References

1. Faries MB. Intralesional Immunotherapy for metastatic melanoma: the oldest and newest treatment in oncology. *Crit Rev Oncog*. 2016;21:65–73.
2. Wiemann B, Starnes CO. Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. *Pharmacol Ther*. 1994;64:529–64.
3. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. *Am J Med Sci*. 1893;105:487–511.
4. Morrissey KM, Yuraszck TM, Li C-C, et al. Immunotherapy and novel combinations in oncology: current landscape, challenges, and opportunities. *Clin Transl Sci*. 2016;9:89–104.
5. Mataraza JM, Gotwals P. Recent advances in immuno-oncology and its application to urological cancers. *BJU Int*. 2016;118: S06–14.
6. Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. *Immunology*. 2007;121:1–14.
7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646–74.
8. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011;480:480–89.
9. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39:1–10.
10. Trombetta ES, Mellman I. Cell biology of antigen processing in vitro and in vivo. *Annu Rev Immunol*. 2005;23:975–1028.
11. Van den Eynde BJ, Boon T. Tumor antigens recognized by T lymphocytes. *Int J Clin Lab Res*. 1997;27:81–6.
12. Darrasse-Jèze G, Deroubaix S, Mouquet H, et al. Feedback control of regulatory T cell homeostasis by dendritic cells in vivo. *J Exp Med*. 2009;206:1853–62.
13. Kober J, Leitner J, Klausner C, et al. The capacity of the TNF family members 4-1BBL, OX40L, CD70, GITRL, CD30L and LIGHT to costimulate human T cells. *Eur J Immunol*. 2008;38:2678–88.
14. Croft M, So T, Duan W, et al. The significance of OX40 and OX40L to T-cell biology and immune disease. *Immunol Rev*. 2009;229:173–91.
15. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. *Nat Rev Immunol*. 2004;4: 762–74.
16. Marigo I, Dolcetti L, Serafini P, et al. Tumor-induced tolerance and immune suppression by myeloid derived suppressor cells. *Immunol Rev*. 2008;222:162–79.
17. Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. *Cancer Immunol Immunother*. 2005;54:307–14.
18. Bouzin C, Brouet A, De Vriese J, et al. Effects of vascular endothelial growth factor on the lymphocyte-endothelium interactions: identification of caveolin-1 and nitric oxide as control points of endothelial cell anergy. *J Immunol*. 2007;178:1505–11.
19. Facciabene A, Peng X, Hagemann IS, et al. Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and T(reg) cells. *Nature*. 2011;475:226–30.
20. Takeuchi Y, Nishikawa H. Roles of regulatory T cells in cancer immunity. *Int Immunol*. 2016;28:401–9.
21. Ohta A. A Metabolic Immune checkpoint: adenosine in tumor microenvironment. *Front Immunol*. 2016;7:109.
22. Kamta J, Chaar M, Ande A, et al. Advancing cancer therapy with present and



- emerging immuno-oncology approaches. *Front Oncol.* 2017;7:64.
23. Galluzzi L, Vacchelli E, Bravo-San Pedro J-M, et al. Classification of current anticancer immunotherapies. *Oncotarget.* 2014;5:12472–508.
  24. Kokate R. A systematic overview of cancer immunotherapy: an emerging therapy. *Pharm Pharmacol Int J.* 2017;5:1–6.
  25. Prowell TM, Theoret MR, Pazdur R. Seamless oncology-drug development. *N Engl J Med.* 2016;374:2001–3.
  26. Menis J, Litière S, Tryfonidis K, et al. The European Organization for Research and Treatment of Cancer perspective on designing clinical trials with immune therapeutics. *Ann Transl Med.* 2016;4:267.
  27. Emens LA, Butterfield LH, Hodi FS, et al. Cancer immunotherapy trials: leading a paradigm shift in drug development. *J Immunother Cancer.* 2016;4:42.
  28. Hodi FS, O'Day SJ, McDermott DE, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363:711–23.
  29. Kohrt HE, Tumei PC, Benson D, et al. Immunodynamics: a cancer immunotherapy trials network review of immune monitoring in immuno-oncology clinical trials. *J Immunother Cancer.* 2016;4:15.
  30. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer Oxf Engl.* 1990 2009;45:228–47.
  31. Nishino M, Jagannathan JP, Ramaiya NH, et al. Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. *AJR Am J Roentgenol.* 2010;195:281–9.
  32. Le Lay J, Jarraya H, Lebellec L, et al. irRECIST and iRECIST: the devil is in the details. *Ann Oncol Off J Eur Soc Med Oncol.* 2017;28:1676–8.
  33. Tazdait M, Mezquita L, Lahmar J, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. *Eur J Cancer Oxf Engl.* 2017;88:38–47.
  34. Ades F, Yamaguchi N. WHO, RECIST, and immune-related response criteria: is it time to revisit pembrolizumab results? *Ecancermedicallscience.* 2015;9:604.
  35. Hodi FS, Hwu W-J, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol Off J Am Soc Clin Oncol.* 2016;34:1510–7.
  36. Wang P-F, Chen Y, Song S-Y, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. *Front Pharmacol.* 2017;8:730.
  37. Haanen JB a. G, Carbone F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol.* 2017;28:iv119-iv142.
  38. Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs.* 2010;14: E10–21.
  39. Roselló S, Blasco I, García Fabregat L, et al. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. *Ann Oncol Off J Eur Soc Med Oncol.* 2017;28:iv100-iv118.
  40. Regis SM. Patient navigation in immuno-oncology. *Am J Manag Care.* 2017;23:SP46–7.
  41. Herbst RS, Soria J-C, Kowanzet M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature.* 2014;515:563–7.

# Changing methods to assess targeted therapies in oncology

Trevor Stanbury<sup>1</sup>, Xavier Paoletti<sup>2</sup>, and Bernard Asselain<sup>3</sup>

1 UNICANCER, Paris, France

2 OncoStat, Gustave Roussy, Villejuif, France

3 Université Paris Sud et Comité statistique de ARCAGY-GINECO, Orsay, France

## Correspondence to:

Trevor Stanbury  
UNICANCER  
101 rue de Tolbiac  
Paris, France 75654  
+33 (0)1 44 23 55 67  
t-stanbury@unicancer.fr

With permission from the journal and authors, this article was adapted and translated from the original French article: Asselain B, Paoletti X. Enjeux méthodologiques de la médecine de précision en oncologie. *Innov Ther Oncol.* 2017;3:33–8. doi: 10.1684/ito.2017.0071.

## Abstract

New methods have been developed to evaluate targeted therapies, since the classic sequence – phase I, toxicity; phase II, efficacy; phase III, comparison with standard treatment – is no longer effective for evaluating these new treatments. In traditional cytotoxic chemotherapy trials, we observe a positive correlation between dose toxicity and dose efficacy. In targeted therapy trials, however, high doses can sometimes be well tolerated and increasing the dose beyond a certain level does not increase tumour response. Early clinical trials in targeted therapies therefore need to

simultaneously assess toxicity and provide early signals of efficacy, based on biomarkers when available. Phase II primary endpoints have also been questioned, since the RECIST (Response Evaluation Criteria in Solid Tumour) is not well suited to functional modifications in tumours. New phase III trials, with more homogeneous targeted populations, are using more flexible designs, including interim analyses and adaptive designs. These flexible designs allow the sample size, and sometimes the trial design, to be modified during the trial. This article discusses these new methodological challenges for evaluating targeted therapies.

Targeted therapies, unlike traditional cytotoxic chemotherapies, block specific pathways/mechanisms by which tumours grow and/or inhibit our immune system from responding. These therapies can target cancer cells or our immune cells (immunotherapies). Gefitinib and cetuximab, as examples, block the epidermal

growth factor receptor (EGFR) signalling pathway on tumour cells. This interferes with the tumour signals that result in tumour growth, proliferation, and migration. Similarly, immunotherapies, such as pembrolizumab, bind to lymphocytes, interfering with the programmed cell death 1 (PD-1)/ programmed death-



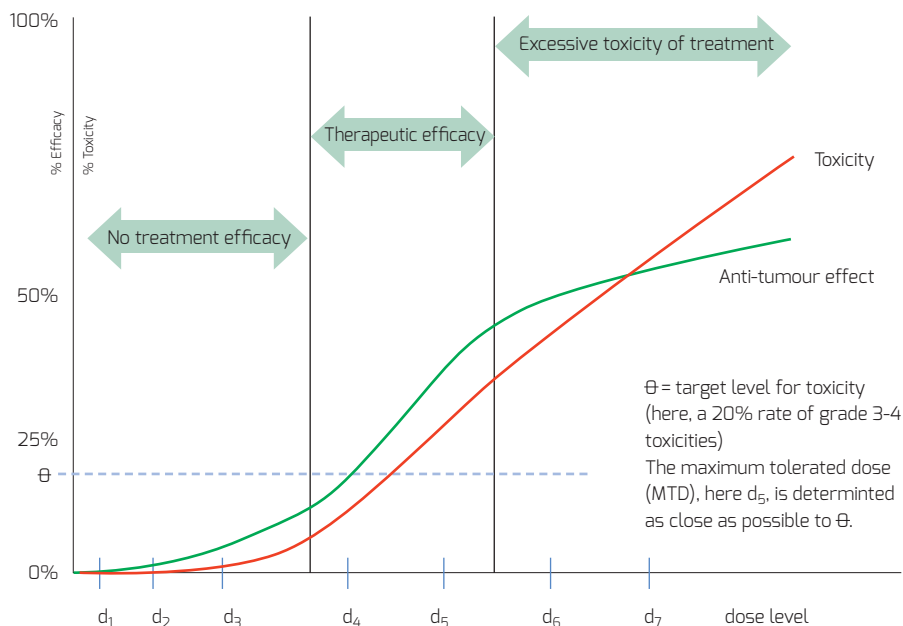
ligand 1 (PD-L1) checkpoint signalling pathway, preventing tumour cells from deactivating the immune response.

The arrival of targeted therapies, including immunotherapies, in oncology has required a re-evaluation of the classical methods used over the last 50 years. The classical sequence consists of identification of the maximum tolerated dose (MTD) and the recommended dose during phase I, selection of the most promising molecules based on the activity (response rate) in phase II, and comparison with standard treatment in phase III. This sequence was developed for cytotoxic chemotherapies and is not optimal for targeted therapies.

In this article, we examine the changes adopted in each of the clinical study phases (I-III) and discuss these new methods for evaluating targeted therapies.

### Phase I studies

The aim of a classical phase I studies, to assess cytotoxic chemotherapies, is to determine the MTD and a recommended phase II dose, and obtain an initial safety profile. These classical phase I dose escalation studies assume that an increase in the treatment dose will increase toxicity and activity (Figure 1).



**Figure 1. The relationship between dose-toxicity and effective dose in classical phase I clinical trials**

This assumption allows us to identify a “therapeutic area” with acceptable toxicity and probable activity. We can identify this “therapeutic area” using different methods,<sup>1</sup> including:

- The “3+3” method that targets a MTD with a toxicity of 33% (i.e. with two patients out of six having a treatment-related side-effect);
- The continuous reassessment method that is more flexible. In this method, we establish a target toxicity level, usually 25% to 30%, before the study.

With the MTD identified, the recommended phase II dose is established, often corresponding to the dose level just below the MTD.

The following issues arise when we use this classical phase I methodology to evaluate targeted therapies. As mentioned, the targeted therapy dose does not always correlate with toxicity and activity. Because of the

low toxicity of some targeted therapies, in about 25% of phase I targeted therapy studies, the MTDs are never reached despite using high dose levels.<sup>2</sup> The toxicity that does occur can also be relatively independent of dose. Concerning activity, once the drug’s target is saturated, an increase in dose will not usually increase activity. The objective of a phase I targeted therapy study is to identify a biological active dose with minimum toxicity and not the MTD as for classical phase I studies.

Identifying the biologically active dose instead of the MTD at first seems interesting, but remains theoretical when the activity on the target is difficult to measure, particularly when biomarkers to measure the saturation of the drug target are not available. When biomarkers are available, their levels do not always correlate with a clinical benefit for patients, suggesting a more complex mode of action than expected. In addition, the use of biomarkers often requires repetitive tumour sampling, which may not be acceptable. Currently, less-invasive or non-

However, phase I targeted therapy studies in oncology simultaneously evaluate tolerance/ toxicity and activity.

invasive methods to monitor tumour evolution are being developed. These include functional imaging to assess tumour perfusion, heterogeneity, and texture, and to quantify angiogenesis (the development of blood vessels for tumours), and liquid biopsies (for example, blood sampling) to assess circulating tumour cells. This research may allow us to better evaluate drug activity independently of toxicity.

Classical phase I studies for cytotoxic chemotherapies were not designed to assess activity. However, phase I targeted therapy studies in oncology simultaneously evaluate tolerance/ toxicity and activity. The targeted therapy studies have fewer dose levels with more patients at each dose level, compared to classical phase I studies. However, phase I targeted therapy studies need to limit the number of patients to a few tens and limit the number and size of extension cohorts. These cohorts, evalu-



ating targeted therapies, can reach hundreds, sometimes more than a thousand, patients without any *a priori* decision rules established.<sup>3</sup> Furthermore, the sample sizes used in these phase I expansion cohorts are not always justified.<sup>4</sup> A review of 522 phase I studies performed at the Dana-Farber/Harvard Cancer Center showed that 60% of studies with three or more expansion cohorts had response/activity as an objective without any justification of the sample size.<sup>5</sup> These phase I targeted therapy expansion cohorts should be designed with the same statistical rigour as classical phase II studies.

## Phase II studies

Phase II studies aim to establish whether a drug at the biologically active dose has clinical efficacy with sufficient tolerance to continue to phase III. The phase II studies of cytotoxic chemotherapies are often single-arm studies that assess response rates over a short time period. To measure treatment activity, we often use the change in the dimensions of the tumour lesions, using imaging (CT scan or MRI scan) assessed by response criteria. These response criteria have evolved over the last 20 years, from the World Health Organization (WHO) classification to the response criteria in solid tumours (RECIST) classification version 1.0, recently upgraded to version 1.1.

These criteria, based on tumour dimensions, are not ideal for evaluating targeted therapies. For example, with inhibitors of angiogenesis, the size of the targeted lesions can be unchanged, while the density and texture can change substantially, particularly due to intra-tumour necrosis.

In studies of new immunotherapies that inhibit immune checkpoints (PD-1/PD-L1) we can see an initial temporary increase in tumour size (pseudo-progression), most probably due to lymphocyte infiltration and tumour swelling.

Thus to evaluate tumour response with targeted therapies, we need to revise the established classifications. The new propositions, e.g., Choi criteria for the tyrosine kinase inhibitors, ir-RECIST and i-RECIST for immunotherapies, do not have an international consensus, and need validation before they can be widely used.

Most phase II oncology studies assess treatment activity based on the response rate (best response obtained or response at a given certain time). The hypotheses are generated using an already established response rate at a given time. The Simon and Fleming trial designs

define a minimum response rate below which the treatment will be considered not effective (null hypothesis) and a targeted response rate (alternative hypothesis) that indicates sufficient activity to progress to phase III studies.

The Simon method was adapted by Bryant and Day<sup>6</sup> to simultaneously account for efficacy and toxicity. In the Bryant and Day method, the treatment is considered not of interest if the response is inadequate or if the toxicity is excessive.<sup>7</sup> The Bryant and Day method can be used to evaluate certain targeted therapies, e.g. immunotherapies, as well as combinations of targeted therapies or targeted therapies associated with cytotoxic chemotherapies and/or radiotherapy.

In phase II oncology clinical studies, progression-free survival (PFS) has become the preferred endpoint since the delay for analysis is substantially shorter than for overall survival (OS) and the interference by “salvage” therapies is limited.<sup>7</sup> In cancers where the patients’ life expectancies are short, i.e. OS is very short, and/or salvage therapies are ineffective, OS may be the most appropriate endpoint. A single arm design can be considered when the endpoint either based on PFS or OS at a given time point, has a reliable historical control.

However, phase II studies evaluate targeted therapies in patients that will potentially respond to treatment. The patient selection is not only based on disease characteristics (clinical stage and histological type), but also on the tumour’s molecular profile and the presence of biomarkers, if these biomarkers are predictive of response or are suspected to be.

In these studies with a highly selected population, it is very difficult to have a precise reference or historical control for response (e.g., PFS rate).

Therefore, a control group is needed<sup>8</sup> to validate the hypotheses and assess treatment activity. However, we cannot directly compare the control and experimental groups since the statistical power is insufficient, due to the limited number of patients in phase II studies.

Sometimes, comparative phase II randomised studies based on phase III methodology are proposed. These studies accept a high false positive risk (alpha-risk), often in the range of 20%, but sometimes even 40%, to reduce the

number of patients required. Accepting this risk means accepting that two out of five significant differences obtained will be by chance! However, when the treatment is extremely active, this strategy may prove to be more efficient. Marketing authorisation can be granted without doing phase III studies, which are long and expensive.<sup>9</sup> However, there is a large risk of obtaining not significant and unconvincing results, due to the relatively small sample size that lacks statistical power, which may stop the drug development of an active treatment.

Phase II studies, even on a limited number of patients, may identify biomarkers that could predict response, even if this research would be exploratory at this stage of drug development. These exploratory studies will facilitate drug development by increasing our understanding of the underlying biology of targeted therapies.

## Phase III studies

Phase III studies are essential to compare targeted therapies to standard treatment. Targeted therapies can be evaluated as monotherapies, in combination with other targeted therapies, or in association with standard treatments. The comparison with standard treatment is recommended

in these studies, while comparing different targeted therapies or different dosages of the same targeted therapy without a control arm is not recommended. The control arm also allows us to evaluate biomarkers that may predict activity.

When a biomarker is known, or suspected, and the biomarker status available at randomisation, the study should be stratified according to the biomarker. However, this is rarely the case. No biomarker (EGFR or KRAS) analyses were planned in the studies assessing gefitinib in lung cancer<sup>10</sup>

and cetuximab in colorectal cancer (the CRISTAL and PETTAC8 studies).<sup>11,12</sup> Actions were taken retrospectively or during the study on a portion of the population, probably not representative. In these studies, the benefits of randomisation were probably lost and the results difficult to interpret.

Although requiring more patients than in phase II studies, phase III targeted therapy studies can be limited to a few hundred patients. The clinical gain, for instance the decrease in the

The comparison with standard treatment is recommended in phase III targeted therapy studies.

risk of progression or relapse, observed with targeted therapies is far superior to that observed with chemotherapy. We could predict a reduced risk of progression or relapse of 40% (hazard ratio [HR] of 0.6), and even 60% (HR of 0.4). This is an important parameter for calculating the number of patients required. These gains can be even more important considering the highly selected population, for example selecting patients with a specific tumour mutation to evaluate the corresponding targeted therapy. Traditionally, phase III studies evaluated treatments in broader populations, however, phase III targeted therapy studies are often performed in a biologically homogenous subpopulation. In studies comparing targeted therapies to placebo, an unequal randomisation can be used, for example including two-thirds of the patients in the experimental arm and the remaining third in the placebo arm (randomisation 2:1). This minimises the number of patients exposed to the placebo. At equal power, overall about 10% more patients are needed in these studies, but with about 10% to 20% fewer patients receiving placebo. This unequal randomisation allows us to more precisely evaluate the toxicity and efficacy of the targeted treatment in the experimental arm.<sup>8</sup>

These phase III studies will initially concern patients with advanced staged disease, as with classical phase III chemotherapy studies, and the new therapies will have to prove efficacy at the advanced and non-advanced disease stage before being evaluated on patients with a better prognosis – in the adjuvant or neoadjuvant setting.

Phase III studies, like phase II studies, often use the PFS as the primary endpoint to show the advantage of the treatment in delaying disease progression or by stabilising the disease. However, a gain in PFS does not always correlate to gain in overall survival, due to interference caused by salvage treatment after the failure of the experimental treatment.

Furthermore, with targeted therapies we cannot be certain that the results in patients with metastatic disease will extrapolate to those at a less advanced disease stage, e.g., after surgery (adjuvant treatment), as was the case in the studies for the antiangiogenic molecules in localised colorectal cancer. In phase III targeted therapy studies, it is important that the intermediate analyses of efficacy and futility be done

according to strict rules, under the control of independent committees of experts. This may eventually allow us to reach an early conclusion with publication of the results, either positive or negative.

## What methodology is appropriate for evaluating targeted therapies?

### The early phases

We have seen that the methodology of the early phase (I and II) have been questioned: A joint evaluation of the tolerance and the efficacy has become necessary as soon as the optimal dose is established.

Despite toxicity being relatively independent of the localisation and histological type of the tumour, we cannot dissociate these disease characteristics from treatment efficacy. We therefore need to treat a sufficient number of patients with the same type of tumour at an early phase.

We could consider adaptive methodologies, where we randomise patients in a number of treatment arms (with different dose levels) with a control arm, in which we equilibrate the types of tumours in each arm to have an initial idea of the treatment efficacy. The intermediate analyses will allow the selection of one or more of the experimental arms based on the tolerance and biological criteria of efficacy. Patient inclusions could continue in the two or three arms showing the most promise and eventually in the tumour types that seem to be most sensitive. These extension cohorts of a reasonable size will allow a decision on whether or not to proceed to a randomised phase II study with a more “robust” criterion, such as the PFS.

### Adaptive phase III methods

The intermediate analyses, evoked for the phase III studies, are a first step towards more flexible methods. The new adaptive methods will allow modification during studies.

Adaptive randomisation allows us to modify the treatment allocation ratio based on intermediate results during the study. Thus, if the treatment administered in Arm B of a study proves to be more active than that of Arm A during an intermediate analysis, the study could begin randomising more patients in Arm B than A. However, even though this method appears to be promising, it is controversial among statisti-

cians since these modifications may extend the study duration and introduce biases.<sup>8</sup>

These studies continually select a population of patients for which the treatment may have greater efficacy. For example, in a study of an immune checkpoint inhibitor, we could decide to include only patients with a strong PD-L1 expression in the stroma, or we could reinforce this subpopulation in calculating a specific power. In this situation, we could use a procedure of sequential testing (closed testing procedure), where we rank the statistical tests to be done in a hierarchical way (e.g., we only test the effect of the treatment in the enriched subpopulation only if the benefit of the treatment is globally significant). These methods could be based on biomarkers that we strongly suspect to be related to the efficacy of the treatment. However, there are a number of cases where we do not have these associated biomarkers. We could also propose a “therapeutic test” by treating all the patients with the targeted therapy, but only randomise patients who respond or who are stable in a second phase. The comparison of the responders and non-responders in the initial phase may allow the identification of new biomarkers.

If allowed for in the protocol at study design, the number of patients required could be adjusted depending on the intermediate results, reviewed by a committee of independent experts. The use of the estimation of treatment effect in the intermediate analysis most frequently leads to an increase in the number of patients to be included.

The phase II-III study design is another option, which allows initiation of a randomised phase II study that can be extended to a phase III, if the phase II results are positive. The patients included in the phase II would be included in the phase III analysis.

Finally, certain trials go beyond all the traditional classifications of cancers by localisation and histological type, using molecular anomalies to classify patients and to propose for each patient a targeted therapy that is most adapted to their profile. These pilot studies, like the SHIVA study,<sup>13,14</sup> pose new methodological challenges, raising such questions as how many targeted treatments, what combination of strategies, what stopping rules, and how to introduce new treatment arms? Moreover, how can we analyse these data to be able to extract knowledge that we can have confidence in?

## Conclusion

The development of “precision oncology” based on known specific molecular anomalies of tumours and the corresponding therapies targeting these anomalies has caused substantial modification of the methodologies that were developed to evaluate cytotoxic chemotherapies. We can no longer base the evaluation of targeted therapies on the parallel between dose-toxicity and dose-efficacy. Early phase trials need to be adapted to simultaneously evaluate tolerance and initial efficacy of therapies. In addition, some targeted therapies are so well tolerated that the MTD was never reached in phase I studies.

The first-in-human studies are approaching phase II studies, with fewer dose levels but including more patients per level. Extension cohorts established for the most promising dose levels, give an idea of the tolerance and efficacy of different cancer localisations. These extension cohorts need however to remain at a reasonable size, including 10 to 20 patients, with clear statistical decision rules. These early phases need to rapidly establish the therapeutic dose and provide initial efficacy information. The randomised phase II studies will evaluate the degree of treatment activity and allow us to design smaller phase III studies. The flexible methodology used in randomised phase III studies allow for the re-evaluation of the initial hypotheses and modification of the sample size and inclusion criteria to select patients more likely to benefit from the treatment during the study. The intermediate analyses for futility allow the early termination of studies that have an extremely small chance of showing treatment efficacy. However, if these more flexible methods are now permitted, the study conception and the application rules must be clearly defined in the protocol at study design.

It is only by respecting a strict methodology, based on early randomised studies, starting from phase II studies, that we can optimise the investigational methodology to evaluate the large number of targeted therapies tested, with their associations, so that each patient can benefit from the treatment best adapted to the biological profile of their tumour.

## Disclaimers

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

## Conflicts of interest

The authors have no conflicts of interest to disclose.

## References

1. Hansen AR, Graham DM, Pond GR, Siu LL. Phase 1 trial design: is 3 + 3 the best? *Cancer Control*. 2014;21(3):200–8.
2. Postel-Vinay S, Gomez-Roca C, Molife LR, Anghan B, Levy A, Judson I, et al. Phase I trials of molecularly targeted agents: should we pay more attention to late toxicities? *J Clin Oncol*. 2011;29(13):1728–35.
3. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384(9948):1109–17.
4. Menis J, Litiere S, Tryfonidis K, Golfopoulos V. The European Organization for Research and Treatment of Cancer perspective on designing clinical trials with immune therapeutics. *Ann Transl Med*. 2016;4(14):267.
5. Dahlberg SE, Shapiro GI, Clark JW, Johnson BE. Evaluation of statistical designs in phase I expansion cohorts: the Dana-Farber/Harvard Cancer Center experience. *J Natl Cancer Inst*. 2014;106(7).
6. Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase II clinical trials. *Biometrics*. 1995;51(4):1372–83.
7. Rubinstein L. Phase II design: history and evolution. *Chin Clin Oncol*. 2014;3(4):48.
8. Saad ED, Paoletti X, Burzykowski T, Buyse M. Precision medicine needs randomized clinical trials. *Nat Rev Clin Oncol*. 2017;14(5):317–23.
9. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382–92.
10. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947–57.
11. Van Cutsem E, Lenz HJ, Kohne CH, Heinemann V, Tejpar S, Melezinek I, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol*. 2015;33(7):692–700.
12. Taieb J, Taberero J, Mini E, Subtil F, Folprecht G, Van Laethem JL, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(8):862–73.
13. Paoletti X, Asselain B, Kamal M, Servant N, Huppe P, Bieche I, et al. Design and statistical principles of the SHIVA trial. *Chin Clin Oncol*. 2015;4(3):32.
14. Le Tourneau C, Kamal M, Tredan O, Delord JP, Campone M, Goncalves A, et al. Designs and challenges for personalized medicine studies in oncology: focus on the SHIVA trial. *Target Oncol*. 2012;7(4):253–65.

## Author information

**Trevor Stanbury, PhD**, is a medical writer at UNICANCER, based in Paris, specialising in writing for oncology clinical studies, including protocols, clinical study reports, and publications. He has a background in organic chemistry. For the last 11 years he has been working in clinical studies and exclusively in oncology for the last 5 years

**Bernard Asselain, MD, PhD**, is the former head of Biostatistics department at the Institut Curie in Paris and is now working in the field of ovarian cancers in the GINECO group in Paris. He has been involved in the methodology of oncology clinical trials for more than three decades.

**Xavier Paoletti, PhD**, is a senior biostatistician, working in the Oncostat Department at Gustave Roussy Institute in Villejuif. He is involved in the field of early phase clinical trials in oncology and has published many papers on phase I trials. He is also involved in the field of meta-analyses and he recently organised a symposium on adaptive methods in clinical trials.



# HIV vaccine clinical trials: An overview

**Jackline Odhiambo**

HIV Vaccine Trials Network  
Cape Town, South Africa

## Correspondence to:

Jackline Odhiambo  
Hutchinson Centre Research Institute  
of South Africa (HCRISA)  
First Floor, Wembley Square 3  
McKenzie Street, Gardens  
Cape Town 8001, South Africa  
+27 76 302 5393  
jodhiamb@hcrisa.org.za

## Abstract

More than 30 years after the discovery of the human immunodeficiency virus as the agent that causes AIDS, an effective vaccine against this deadly disease has yet to be developed. The pathway to the development of a vaccine has been riddled with challenges, many unique to HIV itself. As a result, advocates, scientists, and funders have had to move away from a “home run” philosophy that had anticipated early success. Nonetheless, much has been learned along the way about the genetic diversity of the virus, the limitations of animal studies, and the cultural infrastructure and regulatory challenges involved in testing HIV vaccines. The application of coordinated approaches to face the difficulties outlined in this article is a logical way forward in developing a vaccine. Then even more progress can be made, in spite of all the uncertainties, toward the achievement of a successful vaccine.

A vaccine is a substance that teaches the body's immune system to recognise and defend against harmful viruses or bacteria by stimulating the production of specific antibodies and thereby producing immunity to a disease.<sup>1</sup> Vaccines are prepared from the disease pathogen or its products, or from synthetic substitutes that act like antigens without inducing disease; vaccines are typically administered through injections, orally, or by aerosol.

Vaccines are the most safe and cost-effective way to prevent and eliminate infectious diseases, disability, and death. Preventive/prophylactic vaccines given before exposure to a disease enable the body to build protective mechanisms against infection when one is still healthy, therefore averting future illness. Examples include vaccines against meningitis, influenza, polio, smallpox, measles, rubella, and hepatitis. A vaccine against the human immunodeficiency virus (HIV) would be no exception in terms of impact in the fight against this pandemic.<sup>1</sup> A therapeutic vaccine (which treats disease in individuals who are infected by stimulating the immune system to target diseased cells, thereby improving immune response and enabling the body to curb or exterminate a pathogen) would also have an impact against HIV by reducing the infectiousness (viral load) of those already infected.

HIV, the pathogen that causes AIDS, can be transmitted when a person's body fluids (blood, genital secretions) come into contact with those of an infected person, through sexual contact (the main way the disease spreads) or by needle-sharing amongst intravenous drug users. HIV impairs the immune system over time leading to AIDS. When the body's white blood cells are destroyed, the ability to fight off other diseases is compromised. Active treatment with anti-retroviral (ARV) drugs, which help to maintain or restore immune function, can keep people healthy for years. To manage and end the spread of HIV, a variety of highly effective preventive strategies, best used in combination, is required. A comprehensive toolkit to prevent HIV transmission would include the use of ARVs (antiretroviral therapy as prevention (TAsP) to minimize the infectiousness of HIV-infected persons, Pre-Exposure Prophylaxis (PrEP), Post-



Exposure Prophylaxis (PEP)), behavioural changes, male circumcision, microbicides, needle/syringe exchange programs, and a vaccine, among other strategies.<sup>2</sup> If inoculation with a HIV vaccine reduces the number of people who become infected with HIV, there will be a significant decrease in the number of people in the population who can pass the virus on to others. By preventing future infections, spread of the disease can be halted, and in the process, save millions of lives. Even if the vaccine were of low efficacy and with limited coverage, the effect would still be significant from a public health perspective.<sup>3</sup> Vaccines are the only prevention modality that do not rely on sustained behaviour modification.<sup>4</sup>

Although researchers have been working for many years to develop a vaccine that would treat or prevent HIV infection, little headway has been made. Many potential vaccines have been developed in the past, but none have been good enough for approval. (For information on past and current preventive HIV vaccine trials, see <http://www.iavi.org/trials-database/>). This is because of numerous challenges experienced in creating a successful HIV vaccine, including the fact that this lentivirus mutates much faster than other viruses, thereby making it difficult to target.<sup>5</sup> Another reason is that HIV targets the immune system, which is the very thing a vaccine would try to trigger to elicit protection, so

developing a vaccine to activate the immune system without adversely affecting it like the virus would is not an easy task.<sup>5</sup> The issue of waning immunity over time after receipt of a vaccine is another challenge.<sup>4</sup> In short, for an HIV vaccine to be considered successful, it would have to substantially affect acquisition of infection (if preventive), progression of disease among the already infected, or the infectiousness of the infected (if therapeutic).<sup>6</sup>

### HIV vaccine development and trials

The process of HIV vaccine development, testing, and regulation follows much the same pathway as that of other vaccines, with the stages outlined in Table 1.

### Factors to consider for HIV vaccine studies

#### Developmental strategy complexities

HIV vaccine development is a challenging, complex, and lengthy process, scientifically and operationally. The number of participants in vaccine clinical trials is usually greater than in non-vaccine drug trials because vaccines are generally tested more thoroughly, and scrutiny by approval bodies is more intense.<sup>9</sup> The time and cost resource requirements of testing these vaccines deters investment in vaccine development by manufacturers; such investment is

perceived as risky,<sup>10</sup> even more so for HIV.

Successful development of effective HIV preventive and/or therapeutic vaccines requires that many different candidate vaccines be studied simultaneously in different populations around the world. Research is currently underway on different HIV immunisation concepts/modalities for efficacy based on non-human primate studies and results from earlier trials, as summarised in Table 2.

Additionally, in Africa, the region hardest hit by the epidemic, HIV vaccine clinical trials face unique community, ethical, political, regulatory, and scientific challenges.<sup>16</sup> These challenges include weak or vaccine research-inexperienced national regulatory authorities (RAs), inadequately resourced institutions, undeveloped clinical and laboratory infrastructure, and sub-standard participant recruitment strategies that may exploit communities with high rates of illiteracy.

Given these considerations, no entity can single-handedly overcome the hurdles associated with HIV vaccine development. Indeed there is an urgent ethical need for global support, political will, and collaboration to find a HIV vaccine. This necessitates significant international cooperation over time, drawing on partners from various health sectors, intergovernmental organisations, government, research institutions, industry, and affected populations.<sup>4</sup> Countries with scientific expertise and resources must assist countries that lack infrastructure and regulatory and ethical capacity to conduct trials.

#### Infrastructure and oversight needs

Research sites with insufficient infrastructure often need time to develop facilities (clinic, laboratory, and human capacity), which can take some years to achieve – something to be factored in while building developmental strategies to ensure host countries and communities can meaningfully participate in vaccine development, ensure scientific and ethical conduct of vaccine studies, and function as equal partners with other stakeholders in a collaborative process. To facilitate timely approvals of research, regulatory expertise may also need to be strengthened. Regional regulatory harmonisation could hasten the process and enable a wide knowledge-sharing base. The WHO-supported African Vaccine Regulatory Forum (AVAREF) is one such



Table 1. HIV vaccine development pathway

Stage	Description	Additional Notes
Exploratory <sup>5</sup>	<ul style="list-style-type: none"> <li>● Basic laboratory research conducted by academic or government researchers</li> <li>● Discovery of natural or synthetic antigens that might help prevent HIV or modify effects of the virus.</li> <li>● Antigens may include virus-like particles (made in the lab for preventive vaccines), or other substances derived from HIV.</li> <li>● Duration: 2 to 4 years.</li> </ul>	
Pre-clinical studies <sup>4,5</sup>	<ul style="list-style-type: none"> <li>● Conducted by biopharmaceutical companies.</li> <li>● Tissue-/cell-culture systems used to assess safety/potential toxicities of candidate vaccine &amp;, crucially, its immunogenicity (ability to induce an immune response).</li> <li>● Extensive animal testing (challenge studies) also done, involving NHPs, or non-human primates (monkeys), and other animals. Usually shed some light on cellular responses that might be expected in human beings (though protection using these models of prediction has been particularly difficult with candidate HIV vaccines so far).</li> <li>● May test for safe starting dose for next phase of research &amp; a safe way to administer the vaccine. Injections, including biojectors (needle-free injections) and infusions have been tested.</li> <li>● Duration: 1 to 2 years.</li> <li>● Successful candidate vaccines proceed to clinical studies.</li> </ul>	<ul style="list-style-type: none"> <li>● Adjuvant (substance that enhances magnitude &amp; durability of immune responses elicited by vaccine) may be added to potential vaccine to make it more effective.</li> <li>● Prime-boost technique of vaccination is being studied, where booster doses are given following vaccination with primary vaccine to prolong durability of protection (peak immunogenicity) to counteract inadequacy of primary vaccination alone (waning effect).</li> <li>● Many candidate vaccines flop at this stage as they do not induce desired immune response.<sup>4</sup></li> </ul>
Clinical development <sup>5,6,7,8</sup>	<ul style="list-style-type: none"> <li>● Does not involve vaccinating human subjects &amp; then intentionally exposing them to HIV.</li> <li>● Starts with Investigational New Drug (IND) application by study sponsor (typically a private company) to a Regulatory Authorities (RA) of country(ies) in which vaccine may be marketed.</li> <li>● Study also subject to ethical review.</li> <li>● Vaccine, like other drugs, undergoes a series of clinical trials, Phase I to IV:</li> </ul> <p><i>Phase I</i></p> <ul style="list-style-type: none"> <li>● Involves a small number of adult participants (20-80) who are at low risk for HIV acquisition.</li> <li>● Conducted to assess safety in humans (tolerability, dose ranges) &amp; determine immunization regimens.</li> <li>● Follow-up for adverse effects and/or vaccine reactogenicity (local or systemic signs &amp; symptoms post-vaccination like pain, swelling, redness at injection site, fever, malaise etc.).</li> <li>● Blood samples also drawn to estimate preliminary immunogenicity (type and extent) to HIV elicited by vaccine.</li> <li>● Responses may or may not be protective against HIV; larger trials needed to determine this.</li> <li>● Promising results lead to next testing phase.</li> </ul>	<ul style="list-style-type: none"> <li>● Information about experimental vaccine, risks and benefits of study participation, participant rights &amp; responsibilities is given before seeking consent from potential participants, &amp; throughout trial participation.</li> <li>● IND application includes: description of the vaccine manufacturing &amp; testing processes, summary of the laboratory reports, and clinical study proposal.</li> <li>● Study must have both ethical &amp; regulatory approvals prior to commencement.</li> <li>● The nature of each adverse event is defined in a standardised manner e.g. Injection site pain.</li> <li>● Immunogenicity analysis include measurements of antibody levels &amp; cell-mediated immunity.</li> <li>● Studies may be blinded or open-label.</li> </ul>

Continued on next page

## HIV vaccine clinical trials – an overview – Odhiambo

Table 1. (Continued)

Stage	Description	Additional Notes
Exploratory <sup>5</sup>	<p><i>Phase II</i></p> <ul style="list-style-type: none"> <li>● Involves up to several hundred participants. May include some individuals at higher risk for HIV acquisition.</li> <li>● Purpose is to collect more safety data and more detailed assessment of immune responses.</li> <li>● In Phase IIb studies, more emphasis placed on estimating efficacy.</li> <li>● Randomized, double-blind, placebo-controlled, parallel group design is mostly used.</li> <li>● Successful candidate vaccines move on to larger trials.</li> </ul>	<ul style="list-style-type: none"> <li>● Dosing data is collected; best immunisation schedule is determined.</li> <li>● Best method of vaccine delivery also investigated.</li> </ul>
Approval and Licensure <sup>5,7</sup>	<ul style="list-style-type: none"> <li>● After successful phase 3 trial proving efficacy, the vaccine would go through an approvals process for licensure.</li> <li>● Sponsor submits a Biologics License Application [BLA] to the Regulatory Authorities (RAs).</li> <li>● RA will conduct an inspection of the vaccine’s manufacturing facility and approve the product labelling of the vaccine following usability testing.</li> </ul>	
Post-Marketing Surveillance <sup>5</sup>	<ul style="list-style-type: none"> <li>● Similar to other drugs/vaccines, various systems would be used to monitor the licensed HIV vaccine: <ul style="list-style-type: none"> <li>● adverse event reporting system &amp; database that health care providers and consumers can report a suspected side effect into (pharmacovigilance).</li> <li>● continuous inspection of the HIV vaccine manufacturing facilities by RAs.</li> <li>● review or conduct of batch tests by RAs to ensure the vaccine is consistently safe for public use, unadulterated and efficacious.</li> <li>● phase IV trials.</li> </ul> </li> </ul> <p><i>Phase III</i></p> <ul style="list-style-type: none"> <li>● Large trials involving thousands of people (high risk participants).</li> <li>● Usually a public-private partnership.</li> <li>● Incidence data in regions where vaccine will get tested is gathered when designing study, to inform sample size calculation &amp; duration of follow-up, e.g. with an incidence of HIV of 1.5% per year in a population, ~5,000 volunteers would be needed to adequately power the study.</li> <li>● HIV infection in the population is 1.5% per year</li> <li>● Tests whether experimental vaccine: <ul style="list-style-type: none"> <li>● provides any protection against HIV infection, i.e. vaccine efficacy (VE),</li> <li>● delays progression to AIDS should one get infected (by checking viral load or CD4 count),</li> <li>● causes production of antibodies to HIV or other types of immune responses.</li> </ul> </li> <li>● Also assesses HIV vaccine safety in a large group of people for rare adverse effects.</li> <li>● Randomised, double-blind, placebo-controlled, parallel group trial design.</li> <li>● Study follow-up usually for 2 to 3 years. Participants receive regular HIV testing &amp; risk reduction counselling. That the vaccine is experimental and not yet proven effective is emphasized to study participants.</li> <li>● The questions of whether, and how well, the vaccine works should ideally be answered by a well-designed, well-planned, well-executed and well-controlled efficacy trial, with a statistically significant result. However, reality with HIV vaccines is that may need to do more than just one phase III trial with the same candidate.</li> </ul> <p><i>Phase IV</i></p> <ul style="list-style-type: none"> <li>● Vaccine license-holder might elect to conduct these studies once vaccine is approved and in the market.</li> <li>● Purpose would be to continue to test for vaccine safety, efficacy &amp; other potential issues.</li> </ul>	<ul style="list-style-type: none"> <li>● Key beneficial effects of an HIV vaccine may not be realized directly to vaccinees directly, but at a population level through indirect effects (e.g. reduced infectiousness of infected vaccinees), which are not captured by typical efficacy trial endpoints.</li> <li>● Higher the incidence, lower the number of participants and/or shorter the follow-up period.<sup>5</sup></li> <li>● Assumption is that most participants will be exposed to HIV (unprotected sex, needle sharing) during follow-up in study.</li> <li>● VE evaluated by comparing rate of HIV infection in active vaccine study arm with that in placebo arm. Differences detected, are further analysed to investigate whether due to chance or attributable to vaccine. Normal saline solution or some other inactive substance may be used as placebo.</li> </ul>

initiative to build regulatory capacity where there is limited framework to approve vaccine studies. WHO also supports the Developing Country Vaccine Regulatory Network (DCVRN) in strengthening national RAs in low- and middle-income countries where vaccines are manufactured.<sup>4,5,17,18</sup>

**Community engagement**

Local communities are often keen to be credible partners in HIV vaccine research efforts. To ensure sound ethics, scientific quality, relevance, and acceptability of the proposed research in the affected community, local representatives should be approached early; their involvement in the design, development, implementation, and distribution of results of HIV vaccine research should be sustained throughout. Community support on all these fronts is crucial.<sup>17,19</sup>

**Post-trial access**

When developed, HIV vaccines should be made available and affordable to the population in need. Thus, when the research protocol is developed, it should include scientific justification of the selected population, a balance between risk to study participation and potential benefits to that population, and safeguards from potential harm (medical or social) to participants and exploitation of that community. HIV stigma, human rights discrimination (against women, users of injectable drugs, men who have sex with men, and sex workers). Limited healthcare options, limited

ability to understand the study and consent processes, legal factors, weak regulatory framework, and other factors may increase risk of harm to participants, and hamper the accessibility to potential participants.<sup>18</sup>

**Institutional and regulatory oversight of recombinant DNA research**

Institutional Biosafety Committees (IBCs) are responsible for reviewing research that involves recombinant DNA, RNA, other potentially infectious material, and transgenic animals, to provide recommendations on control of biohazards associated with the use of microbiological agents. Since HIV vaccines fall in this category because they could consist of substances derived from HIV or other viruses such as the canarypox, adenovirus, or cytomegalovirus vectors, IBCs must review and approve these studies, in addition to the usual regulatory and ethics permissions. IBCs represent the interests of the local community in terms of public health and the environment.<sup>20</sup>

For similar reasons a HIV vaccine may be subject to approval for use as a genetically modified organism (GMO) product in some countries. For instance, in South Africa yet another layer of approval is required by the Department of Agriculture, Forestry and Fisheries (DAFF) for “intentional introduction of GMOs into the environment.”<sup>21</sup>

**Vaccine manufacturing capacity**

It is vital that a test HIV vaccine for an efficacy trial have consistent batch-to-batch production, with defined, reproducible specifications.<sup>18</sup> It takes time to formulate a fully characterised vaccine, including stability and data regarding immunogenicity (its ability to provoke an immune response). Capacity to produce such a vaccine in large quantities over a certain period is another factor to consider. Adenovirus vector vaccines are popular as vaccine platforms as they satisfy all the above factors.<sup>22</sup>

**Local communities are often keen to be credible partners in HIV vaccine research efforts.**

**Impact of non-vaccine prevention measures on HIV incidence**

Current and future efficacy trials for HIV-1, the most common and infectious type, face practical challenges as effective or partially effective non-vaccine prevention programs<sup>23</sup> with agents such as oral PrEP, are projected to decrease the incidence of HIV-1. This requires consideration during sample size calculation and other study design matters. If there is a decreased incidence of HIV-1, larger cohorts would be needed to power the studies sufficiently for demonstration of efficacy while also assessing safety of the vaccine, so there needs to be a way of monitoring uptake of the prevention programme. Depending on uptake or other events, there may need to be design adjustments

*Table 2. HIV vaccine concepts currently under study for efficacy in humans*

<p><b>Broadly neutralizing monoclonal antibodies (bnmAbs)</b></p>	<ul style="list-style-type: none"> <li>● Discovered from persons who were able to control the virus naturally without the use of ARVs for over 15 years, where antibodies bind to the CD4 cell site that HIV targets.<sup>11</sup></li> <li>● From in vitro studies, it is hoped that bnmAbs like VRC01 can be used to design reasonably efficacious preventive vaccines that give passive immunity in humans against different HIV strains.<sup>12</sup></li> </ul>
<p><b>Vaccines targeting specific HIV-1 strains<sup>a</sup></b></p>	<ul style="list-style-type: none"> <li>● Progress made from the Thai prime-boost trial (RV144).<sup>13</sup></li> <li>● Different HIV-1 subtypes (clades) are found in different regions of the world, e.g. HIV-1 subtype C, found in the Southern Africa population, which is the target for the vCP2438 and Bivalent Subtype C gp120/MF59 prime-boost vaccine regimen.<sup>14</sup></li> </ul>
<p><b>Global vaccine targeting multiple HIV-1 strains</b></p>	<ul style="list-style-type: none"> <li>● Immunogens (proteins) assembled from natural sequences of different prevalent HIV-1 subtypes (collectively known as a mosaic antigen) to increase the range of immune responses for improved coverage (worldwide).<sup>9</sup></li> <li>● Initial proof of concept study with the Ad26.Mos4.HIV (Ad26 vaccine) and Clade C gp140 (protein vaccine) prime-boost regimen, is initially being tested in young women at high risk of HIV infection.<sup>15</sup></li> </ul>

<sup>a</sup>HIV-1 is one of the two types of HIV and the most common. The other type, HIV-2, is relatively uncommon, is less infectious, and has a lower mortality rate.

or modification of endpoints for ongoing studies.

Local reviewing bodies need to be aware of what is considered the standard of HIV prevention in their country, communities, or study populations in order to assure that sponsors address these issues in their trials with stated aims; appropriate ethical standards must also be upheld.<sup>4</sup>

#### **Deficit of appropriate pre-clinical animal models**

Several experimental HIV vaccine approaches in pre-clinical studies have elicited varying degrees of efficacy in non-human primates (chimpanzees, monkeys). Many of these approaches fail in clinical testing, underscoring the fact that although animal models are valuable in various ways, they are yet to be predictive of protection in humans. Therefore, we can then only truly obtain such information from human trials. This limitation should be considered by regulators when reviewing trial applications. As clinical trials are costly (human, financial, materials, laboratory resources), improvement on animal models is warranted.<sup>4,8</sup>

#### **Unknown immunological correlates of HIV/AIDS protection**

While immunogenicity data or a probable mode of action should be provided to justify conducting a HIV vaccine trial, not enough is known currently in the field about the candidate vaccines/regimens/amount of immunogenic response to make rational go/no-go decisions with vaccine development. With most other diseases that can be prevented with vaccines, there is a correlation between the natural or vaccine-induced immune response and the protection against infection/disease. With HIV, a wide range of immune responses are seen when one becomes infected with the virus. Furthermore, these responses do not eradicate all of the infection in the body or prevent progression to AIDS. So not only is there no known reliable correlate of protection, but even the immunological mechanism is still unknown whereby a vaccine might protect, either by preventing the acquisition of disease or by modulating it. Lack of clear scientific criteria to support advancement into efficacy studies is a challenge. An option would be to submit a trial application without these correlates and use the proposed study to identify them. Current HIV vaccine develop-

ment strategies target the induction of both humoral immunity (antibody-mediated protective response involving B lymphocyte cells that recognize pathogens in blood or lymph) and cell-mediated immunity (protective response for pathogen-infected cells, tumor cells, or transplanted cells, following activation of antigen-sensitized T lymphocyte cells).<sup>4,8</sup>

#### **Genetic variation of HIV**

The classification of HIV isolates from different geographical areas into genetic sub-types (clades) has enabled mapping of the epidemiological spread of infection, which has led to the rationale of selecting local isolates from trial sites as the basis of immunogens to be used in vaccine trials, for example subtype B in the Americas, subtype C in Africa, subtype E in Thailand. This heterogeneity in HIV lies particularly in the genes that encode for the gp120 and gp41 proteins. Unique circulating forms can also result from recombination among the different HIV subtypes. Despite this knowledge, it remains unclear what the relationship is between this genetic variability of HIV and any vaccine-induced protection observed. Trial investigations with experimental mosaic vaccines (that use proteins assembled from natural sequences of different prevalent HIV subtypes) may shed some light on this.<sup>4,8,18</sup>

#### **Vaccine-induced seropositivity**

Whereas creating an antibody response is the goal of an HIV vaccine, such a response may lead to a reactive result if a vaccine recipient were to undergo routine HIV testing since these tests usually detect antibodies to HIV in the blood, and not the virus itself. This phenomenon is called vaccine-induced seropositivity (VISP).<sup>24</sup> VISP detection and duration rates vary greatly, depending on the product's potency, durability, dosing, and type of the test being used.

For study participants who receive a VISP-positive result, this can sometimes lead to incorrect diagnoses, which can cause stress and unnecessary complications such as challenges with insurance, military service, blood/tissue donation, immigration, and pregnancy (a false positive antibody test could lead to unnecessary ARV treatment of a baby). Testing outside the study can also lead to unblinding of the participant. This scenario can occur if a "positive" result is obtained during routine testing

conducted outside of the study, followed by in-study HIV-negative test results. When this occurs, it can compromise study data if the participant changes risk behaviour, even if unintentionally. It is therefore necessary for VISP education to emphasise to all participants the importance of getting all HIV testing done through the study or research site until their VISP is no longer detectable. A VISP registry to verify previous study participation and receipt of HIV vaccine product, to promptly facilitate further HIV testing, is indicated.

#### **Reactogenicity data collection**

The collection of data on specific adverse reactions (reactogenicity) after vaccine administration is a study process that must be implemented well. This would usually be in the form of diary cards, which are used to collect participant-recorded data on temperature, injection site reactions such as swelling or redness, among other solicited symptoms. These data contribute to the safety endpoints of vaccine studies, therefore participants need to be well trained on completing and returning the tool (keeping in mind recall bias and varying levels of cognitive abilities among participants) such that accurate and complete data are collected.

#### **Sufficient time for antibody development**

It takes time for sufficient antibodies to develop in the body such that the full protective picture is elicited and can be evaluated. This contributes to the length of time required for trial participant follow-up. If the study is conducted in a population at high risk of acquiring HIV, where more events could occur in a shorter timeframe, this period could potentially be 3 years; the time could be lessened if the sample size is very large. Correlates analyses should be planned prospectively in efficacy trial designs. Timing and frequency of collection of the appropriate specimens post-vaccination and post-infection (serum, plasma, blood cells, mucosal cells), as well as the handling and storage of specimens, must be considered. All HIV infections that occur during prevention trials should be characterized by subtyping and sequencing. Impact of any ARVs (if started) on viral load should be factored in. Of course, all of this need for data should be weighed against the operational costs and logistics of collection (participant study visits, risky or invasive sampling, and sample processing).<sup>4</sup>

### Considerations regarding regulatory bodies

Statistical analysis plans submitted to approvers should be clear from the beginning on various issues including analysis of overall efficacy and subgroup results, timing of unblinding for analysis purposes, modified intention-to-treat analysis (if results are discordant, attention should be paid as to why).

The Informed consent process should relay the paradoxical potential risk to harm, rather than protect (greater risk of infection through risky behaviour or of disease progression in those who become infected), and referral to care if seroconversion occurs.<sup>4,18</sup>

### Conclusion

With HIV vaccine development, what is most important is not whether trials are in a particular phase but rather that studies are designed and carried out in a manner that supports the practice of sound and ethical science. That, ultimately, is what is needed to progress toward the goal of an approved HIV vaccine.<sup>4</sup>

### 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 declares no conflict of interest.

### References

- Hiv.gov. HIV Vaccines. 2017 [cited 2017 Nov 11]. Available from: <https://www.hiv.gov/hiv-basics/hiv-prevention/potential-future-options/hiv-vaccines>.
- Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. *Current HIV/AIDS reports*. 2011;8(1):62–72.
- Stover J, Bollinger L, Hecht R, Williams C, Roca E. The impact of an AIDS vaccine in developing countries: a new model and initial results. *Health Aff*. 2007;26(4):1147–58.
- Sheets RL, Zhou T, Knezevic I. Review of efficacy trials of HIV-1/AIDS vaccines and regulatory lessons learned: a review from a regulatory perspective. *Biologicals*. 2016;44(2):73–89.
- The History of Vaccines: An Educational Resource by The College of Physicians of Philadelphia. *Vaccines for Sexually Transmitted Diseases*. 2017 [cited 2017 Nov 11]. Available from: <https://www.historyofvaccines.org/content/articles/vaccines-sexually-transmitted-diseases>.
- Follmann D, Duerr A, Tabet S, Gilbert P, Moodie Z, Fast P, et al. *J Acquir Immune Defic Syndr*. 2007;44(1):49–60.
- HIV/AIDS vax - An IAVI Report Bulletin. *Understanding Vaccine Trials: How are AIDS vaccines tested?* 2003;1(1):4. Available from: [The Bulletin on AIDS Vaccine Research](http://www.bulletinonaidsvaccine.org). <http://www.vaxreport.org/vax-1-1-august-2003/869-understanding-vaccine-trials>.
- Esparza J. An HIV vaccine: how and when? *Bull World Health Organ*. 2001;79(12):1133–7.
- The History of Vaccines: An Educational Resource by The College of Physicians of Philadelphia. *Vaccine Development, Testing, and Regulation*. 2017 [cited 2017 Nov 04]. Available from: <https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation>.
- Black S. The costs and effectiveness of large Phase III pre-licensure vaccine clinical trials. *Expert Rev Vaccines*. 2015;14(12):1543–8.
- Wu X, Wang C, O'Dell S, Li Y, Keele BF, Yang Z, et al. Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site. *J Virol*. 2012;86(10):5844–56.
- AMP Study. About AMP: What is the AMP Study? 2017 [cited 2017 Nov 30]. Available from: <https://ampstudy.org.za/about>.
- U.S. Military HIV Research Program. RV144 Trial. 2017 [cited 2017 Dec 02]. Available from: <https://www.hivresearch.org/rv144-trial>.
- Uhambo: A Journey of Hope to Prevent HIV. What is HVTN 702? 2017 [cited 2017 Nov 30]. Available from: <http://www.uhambo.org.za/about>.
- Imbokodo: Stand up to HIV. What is Imbokodo? 2017 [cited 2017 Nov 30]. Available from: <https://www.imbokodo.org.za/about>.
- Vardas E, Buttò S, Glashoff R, Malnati MS, Poli G, Clerici M. Preparing for phase II/III HIV vaccine trials in Africa. *Microbes Infect*. 2005;7(14):1436–44.
- UNAIDS Guidance Document: Ethical considerations in HIV preventive vaccine research. 2000
- Scientific considerations for the regulation and clinical evaluation of HIV/AIDS preventive vaccines: report from a WHO-UNAIDS Consultation 13-15 March 2001, Geneva, Switzerland. *AIDS*. 2002;16(10):W15–25.
- Okpokoro E, Osawe S, Datong P, Yakubu A, Ukpom M, Orhii P, et al. Preparing for HIV vaccine trials in Nigeria: building the capacity of the community and national coordinating, regulatory and ethical bodies. *J AIDS Clin Res*. 2013;4(12):260.
- National Institute of Environmental Health Sciences. Institutional Biosafety Committee. 2017 [cited 2017 Dec 03]. Available from: <https://www.niehs.nih.gov/about/boards/ibc/index.cfm>.
- Department of Agriculture, Forestry and Fisheries: Republic of South Africa. Biosafety Notifications. 2017 [cited 2017 Dec 03]. Available from: <http://www.daff.gov.za/daffweb3/Branches/Agricultural-Production-Health-Food-Safety/Genetic-Resources/Biosafety/Biosafety-Clearing-House>.
- Barouch DH, Picker LJ. Novel vaccine vectors for HIV-1. *Nat Rev Microbiol*. 2014;12(11):765–71.
- Excler JL, Michael NL. Lessons from HIV-1 vaccine efficacy trials. *Curr Opin HIV AIDS*. 2016;11(6):607–13.
- HIV Vaccine Trials Network. Getting the Right Test for HIV. [cited 2017 Nov 30]. Available from: <http://www.hvtn.org/en/participants/visp-hiv-testing.html>.

### Author information

**Jackline Odhiambo**, B. Pharm, MSc. Clinical Trials, has held various roles in clinical research since 2009, including quality management. She is a project manager at the HIV Vaccine Trials Network, working with protocol chairs to support study operations and implementation.

# Allergen immunotherapy in the European regulatory environment

Ulrike Lehnigk

Allergopharma GmbH & Co. KG, Reinbek, Germany

## Correspondence to:

Dr. Ulrike Lehnigk  
Allergopharma GmbH & Co. KG  
Hermann-Körner-Str. 52  
21465 Reinbek, Germany  
+49 40 72765-618  
ulrike.lehnigk@allergopharma.com

## Abstract

Allergen immunotherapy (AIT) modulates the immune system to prevent and relieve allergic symptoms. Unlike allergen avoidance and medication to control symptoms, AIT targets the underlying pathophysiology of allergic diseases. AIT is now considered a type of therapeutic vaccination. This article focuses on the current regulatory environment in the EU and the special considerations in designing clinical trials evaluating AIT products.

## Background

Allergen immunotherapy (AIT) modulates the immune system to prevent and relieve allergic symptoms.<sup>1</sup> Unlike allergen avoidance and medication (e.g. antihistamines and corticosteroids)

to control symptoms, AIT targets the underlying pathophysiology of allergic diseases. AIT is now considered a type of therapeutic vaccination because it uses antigens to treat an existing illness by modulating the immune system.

In AIT, allergen is administered subcutaneously or sublingually at regular intervals to modulate the immune response. The aim is to reduce associated symptoms, decrease the need for medication, and prevent the development of new allergies and asthma.<sup>2</sup> Traditionally, AIT products contain allergens isolated from biological sources such as pollen or house dust mites. These can be used unmodified or denatured with aldehydes and may be mixed with an adjuvant.

AIT is indicated in patients whose allergies interfere with daily activities or sleep despite allergen avoidance and medication, who have moderate-to-severe allergic symptoms when exposed to aeroallergen, and who are sensitised to allergen-specific immunoglobulin E.<sup>3</sup> These patients also often have co-existing asthma.

Allergen products for subcutaneous AIT are mainly applied as depot formulations, meaning that the drug is injected as a localised mass. AIT is administered in escalating doses every 7 and 14 days for depot solutions and every 3 to 7 days for aqueous solutions (Figure 1). When the maximum tolerated dose is reached, the injection intervals can be extended to every 4 to 8 weeks. For airway allergies (allergy-induced asthma), the overall duration of subcutaneous AIT should be at least 3 years.<sup>3</sup>

## Regulation of allergen products in the EU

Previously, AIT products were marketed mainly based on expert opinion, and regulatory oversight was limited. However, in the last 20 years, clinical data is increasingly needed to access the market.<sup>4</sup>

In the EU, according to the Directive 2001/83/EC, adopted in 2004, therapeutic allergen products are considered medicinal products, substances, or combination of substances for diagnosing, treating, or preventing a disease.<sup>5</sup> Generally, these products require marketing authorisation to be commercialised.

EU Directive 2001/83/EC greatly advanced the legal framework for allergen products, although market access in EU member states continues to be heterogeneous. According to article 5 of EU Directive 2001/83/EC, allergen products, especially products prepared for specific patients (named patient products (NPPs)), can be prescribed to individuals in EU member states without marketing authorisation.

Many EU member states have passed specific laws adopting EU Directive 2001/83/EC.<sup>4</sup> An example is the *Therapieallergene-Verordnung* (Therapy Allergens Ordinance) in Germany (see Box opposite).

## Clinical development of AIT products in the EU

In the EU, since 1993, with the exception of bee and wasp venom preparations, marketing

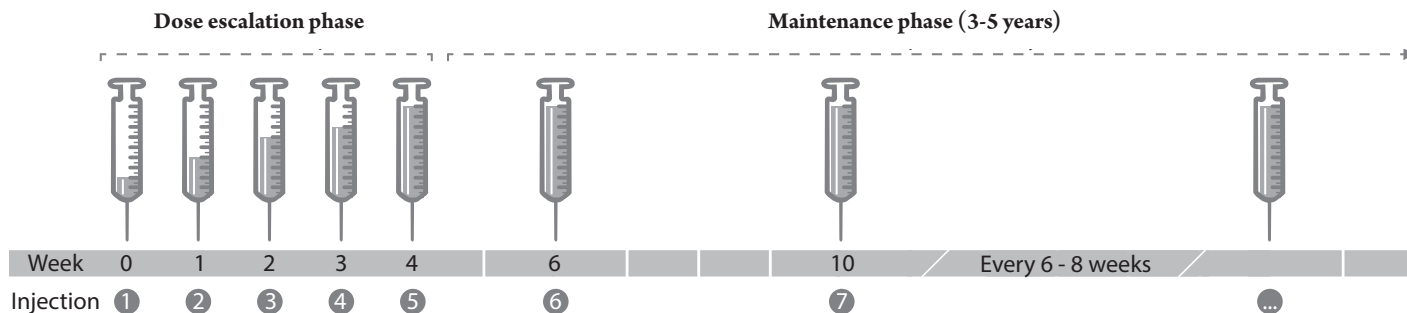


Figure 1. Example of a dosing schedule of subcutaneous AIT

During the dose-escalation phase, increasing doses of the allergen are applied every 7 days for until the maximum tolerated dose is reached. During the maintenance phase, the time between injections can be extended to every 4 to 8 weeks.





authorisation has only been granted if at least one double-blind placebo-controlled trial has been successfully completed. More stringent requirements for AIT clinical trials have resulted in a significant improvement in the quality of the data.<sup>3</sup>

Since 2004, EU member states have had to follow Good Clinical Practice guidelines as established by the Clinical Trials Directive (EU

Directive 2001/20/EC). As a result, many randomised double-blind placebo-controlled trials assessing AIT products have been conducted in recent years. However, because of the seasonal nature of many allergic diseases and the lasting immunological changes induced by AIT, these clinical trials can be very time-consuming and costly, especially if a disease-modifying effect is the intended claim.<sup>4</sup>

In addition, since 2008, AIT clinical trials must be designed according to the Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006).<sup>4,7</sup> This guideline addresses efficacy and safety measures for AIT products based on active substances (e.g. allergen extracts, recombinant allergens, purified native allergens, and modified

## The Therapy Allergens Ordinance in Germany

In 2005, Germany introduced an exemption for NPPs for therapeutic purposes. AIT products manufactured for an individual patient were marketed as NPPs and did not require a marketing authorisation. This was independent of previously authorised products from the same allergenic source.<sup>3</sup>

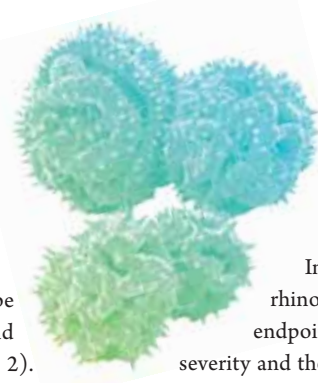
Since 2008, the Therapy Allergens Ordinance has governed AIT products distributed as NPPs and used to treat the most frequent allergies.<sup>3</sup> Individual formulations containing any of the following allergen extracts require marketing authorisation:

- *Poaceae species* (grasses) excluding *Zea mays* (maize)
- *Betula species* (birch)
- *Alnus species* (alder)
- *Corylus species* (hazel)
- *Dermatophagoides species* (house dust mite)
- Bee venom
- Wasp venom

For NPPs that were marketed before the Therapy Allergens Ordinance came into effect, a transition procedure was created. These NPPs can still be distributed while the marketing authorisation application is being processed. This allows companies to conduct clinical trials and compile

full marketing application dossiers to evaluate the efficacy and safety of these products.<sup>2,3</sup> All other allergen extracts, other than those listed above, produced as NPPs do not require marketing authorisation and are not officially monitored for quality, efficacy, and safety, or governmental batch release.

The application for marketing authorisation must include the results of all preclinical and clinical trials, as well as any results from additional testing. AIT products are only authorised for indications and patient groups for which safety and efficacy have been proved.<sup>2</sup>



allergens)<sup>7</sup> and is applicable to clinical trials on AIT regardless of the affected organ system, allergen source, allergen product, or route of administration.

## Considerations for different kinds of AIT clinical studies in the EU according to CHMP/EWP/18504/2006

### Phase I trials

AIT products should only be tested in patients with allergies because healthy individuals do not react to and are not put at risk by exposure to allergens.

### Dose-finding studies

Dose-finding studies include multiple arms each with short-term treatment (e.g. 2 to 4 months) at a different dose. The primary efficacy measure can be a provocation test (e.g. conjunctival, nasal, or bronchial, or whole-body allergen exposure in an allergen challenge chamber) or other clinical endpoint assessing allergy severity.

### Pharmacokinetic and pharmacodynamic studies

Pharmacokinetic and pharmacodynamic studies are not possible for AIT products. Due to the nature of AIT, plasma concentrations of the active substance are usually not measurable. Effects of AIT on the immune system are assessed by changes in allergen-specific IgG levels, T-cell responses, or cytokine production or by changes in the target organ specific response, for example using provocation tests.

### Confirmatory trials

Confirmatory trials on AIT should be performed using a double-blind placebo-controlled design (Figure 2). Generally, statistical superiority compared to placebo or another comparator must be demonstrated. Because local allergic adverse events are frequent with AIT, to maintain blinding, a placebo preparation with histamine should be considered.

Confirmatory trials should enrol only patients with mild symptoms prior to randomisation. Confirmatory trials should include a prospective baseline period with a controlled collection of symptoms and allergen exposure to avoid the effects of variable allergen exposure, for example, during pollen seasons.

For seasonal allergies, for the baseline and evaluation periods, exposure to the relevant allergen must be documented and the minimum pollen count must be defined. For perennial allergies (e.g. to house dust mites), variations of indoor allergen levels must be minimised. For example, cleaning of the patient's home should be completed before the start of the clinical trial and before baseline symptoms are measured. Also, allergen exposure should be documented for each patient.

For allergic rhinoconjunctivitis, the efficacy of AIT can be evaluated in a single pollen season for seasonal allergies or after one or two control periods for perennial allergies. However, a persistent effect due to changes in the immune system can only be demonstrated in long-term trials. Thus, the possible claims of efficacy differ depending on the duration of the trial (Table 1).

In confirmatory trials on allergic rhinoconjunctivitis, the primary endpoint reflects both symptom severity and the intake of rescue medication. Several combined scores that include both severity and rescue medication use have been developed.

Symptom severity is often assessed using patient self-reported symptom scores recorded daily during a defined period. A single harmonised symptom score does not exist for allergic rhinoconjunctivitis, although most trials use a 4-point rating scale to score nasal itching, sneezing, rhinorrhoea, nasal obstruction, ocular itching, grittiness, redness, and ocular tearing (Table 2). Medication use should be scored according to those needed to relieve the magnitude and duration of symptoms (Table 3). Whatever the primary efficacy endpoint chosen, the endpoint and what constitutes a clinically relevant effect should be pre-specified and justified in the study protocol. Secondary endpoints for confirmatory trials can include the total symptom score, the total medication score, individual symptom scores, health-related quality of life (using validated questionnaires), symptom load scored using a visual analogue scale, and symptom-free days.

### Safety

MedDRA is used to code adverse events in AIT trials. Usually, adverse events are graded as mild, moderate, or severe and assessed for relatedness to trial medication. Serious adverse events, especially those related to the treatment, must be described in detail. Expected allergic side-effects are classified according to their timing (immediate or delayed) and the site of appearance

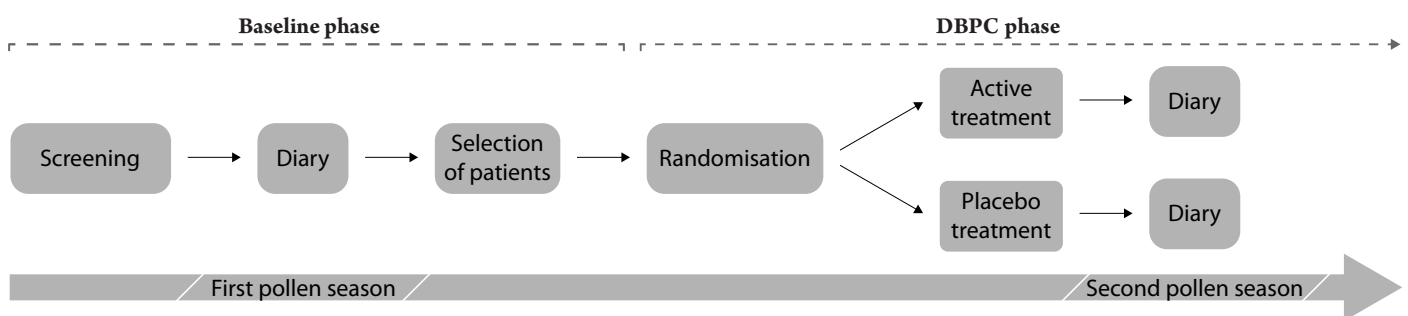


Figure 2. Example flow chart of a randomised double-blind placebo-controlled clinical trial with pollen AIT

During the baseline pollen season, symptoms and used medications of screened patients are assessed using a diary. Patients with a defined minimum level of allergic symptoms are selected for randomisation. Treatment with active therapy or placebo is performed before the following pollen season. Efficacy outcome measures (symptoms and medication use) are assessed during the pollen season using a diary.

**Table 1. Claims for marketing authorisation<sup>7</sup>**

Claim	Efficacy parameter
Treatment of allergic symptoms	Short-term clinical trials to show efficacy in the first pollen season after start of AIT or to show efficacy in perennial allergies after some months of treatment
Sustained clinical effect	Maintenance of significant and clinically relevant efficacy during 2 to 3 treatment years
Long-term efficacy and disease modifying effect	Sustained significant and clinically relevant efficacy in post-treatment years
Curing allergy	Sustained absence of allergic symptoms in post-treatment years

**Table 2. Four-point rating scale for patient allergic symptoms**

Score	Severity	Definition
0	Absent	No symptom evident
1	Mild	Clearly present
		Minimal awareness of symptom Easily tolerated
2	Moderate	Bothersome but tolerable Definite awareness of symptom
		3



Severity is assessed on a scale from 0 to 3 for nasal (sneezing, running, blocked), conjunctival (itching, tear flow, redness) and bronchial symptoms (cough, wheezing, asthma with dyspnoea), giving a possible maximum daily score of 27.<sup>7, 14</sup>

**Table 3. Example for scoring of medication**

Type of medication	Unit	Score
Levocabastine nasal spray	1 puff	0.5
Levocabastine eye drops	1 drop	0.5
Loratadine or cetirizine tablets	10 mg	6
Oral corticosteroid	5 mg prednisolone or equivalent	4
Salbutamol	100 µg	1
Inhaled corticosteroids	400 µg budesonide or equivalent	6

The Medication Score rates the daily consumption of additional anti-allergic drugs according to the type, route and dose or number of applications. The combined Symptom Medication Score is calculated by the daily sum of the documented symptoms and the intake of additional anti-allergic medication.<sup>14</sup>

(local or systemic). Systemic reactions are graded using the European Academy of Allergy and Clinical Immunology or the World Allergy Organisation grading systems.<sup>8,9</sup> Other safety parameters collected in AIT trials include vital signs, routine blood and biochemical tests, and urinalyses.<sup>8</sup>

## Challenges in clinical trials of AIT products

### Patient selection

Because patients with allergic diseases are usually sensitised to more than one allergen group, selecting patients sensitised to a single allergen group is difficult. AIT trials should therefore include patients sensitised to a limited number of allergens, which must be identified and documented. Furthermore, to avoid biasing the outcome for one allergy, patients with concurrent allergies should be excluded, although not all co-sensitisations are clinically relevant. An example where a concurrent allergy may bias results are patients with allergic rhinoconjunctivitis caused by both a seasonal allergen (i.e. pollen) and a perennial allergy caused by animal dander from a pet. For patients with allergic airway disease, a baseline period is recommended before enrolment to ensure minimal symptoms at the start of treatment. Finally, patients should be excluded if they have received an AIT for the investigational allergen or a cross-reacting allergen in the previous 5 years or are receiving AIT for any allergen.

### Unpredictable pollen seasons

Phase 3 AIT trials must be performed under natural allergen exposure, and the primary endpoint must include both symptom and medication scores.<sup>2,10</sup> These trials are also called “field trials”.

The outcome of AIT clinical trials can be influenced by variations in pollen counts between different regions and across different years and the patient’s individual pollen exposure during the pollen season, as well as interfering aero-allergens.<sup>2,11,12</sup> In addition, a patients’ symptoms depend on their sensitivity to the investigated allergen, and they often depend more on the allergen content than on the total pollen load.<sup>11</sup>

Allergen challenge chambers have been used in dose-finding trials and may also be an option for confirmatory trials with allergens with unpredictable pollination and allergen content.

Allergen challenge chambers may be particularly useful in trials conducted over several years or during years with low pollen counts.<sup>2,13</sup> However, the results must be validated in studies assessing effects on allergies due to natural exposure, and the how measuring within or outside the pollen season must be evaluated.

## Conclusion

Since European Directive 2001/83 EC was implemented in 2004, the regulatory environment for AIT products has changed. The requirements for demonstrating quality and efficacy have become stricter, creating new challenges. Despite these advances, market access for these products in the EU remains heterogeneous. Several European initiatives are now working on a harmonised approach to regulate these products.

## Acknowledgements

The author would like to thank colleagues at Allergopharma, Trevor Stanbury (medical writer at R&D Unicancer), and Philip Homann (freelance graphic designer) for assistance.

## Conflicts of interest

The author is employed by Allergopharma GmbH & Co. KG.

## References

1. Pfaar O, Bonini S, Cardona V, Demoly P, Jakub T, Jutel M et al. Perspectives in allergen immunotherapy: 2017 and beyond. *Allergy*. 2018 Jan;73 Suppl 104:5–23.
2. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, van Gerth Wijk R et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy*. 2017 Sep 23. doi:10.1111/all.13317. [Epub ahead of print]
3. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergy and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int*. 2014;23(8):282–319.
4. Bonertz A, Roberts G, Hoefnagel M, Timon M, Slater J, Rabin R et al. Challenges in the implementation of EAACI Guidelines on Allergen Immunotherapy: A global perspective on the regulation of allergen products. *Allergy*. 2017 [cited 2017 Aug 11]. *Allergy*. 2018 Jan;73(1):64–76.
5. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use Official Journal L - 311, 28/11/2004, p. 67-128; 2004.
6. 2001/20/EC D. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. In: Official Journal of the European Communities. 2001. Available at: <https://www.eortc.be/services/doc/clinical-eu-directive-04-april-01.pdf>.
7. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases: European Medicines Agency (EMA). Committee for Medicinal Products of Human Use (CHMP); 2008.
8. Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox L et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language. *J Allergy Clin Immunol*. 2013;132(1):93–8.
9. Cox L, Larenas-Linnemann D, Lockey RE, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol*. 2010;125(3):569–74, 574.e1-574.e7.
10. Pfaar O, Demoly P, van Gerth Wijk R, Bonini S, Bousquet J, Canonica GW et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: An EAACI Position Paper. *Allergy*. 2014;69(7):854–67.
11. Rösner-Friese K, Kaul S, Vieths S, Pfaar O. Environmental exposure chambers in allergen immunotherapy trials: Current status and clinical validation needs. *J Allergy Clin Immunol* 2015;135(3): 636–43.
12. Durham SR, Nelson HS, Nolte H, Bernstein DI, Creticos PS, Li Z et al. Magnitude of efficacy measurements in grass allergy immunotherapy trials is highly dependent on pollen exposure. *Allergy*. 2014;69(5):617–23.
13. Pfaar O, Hohlfeld JM, Al-Kadah B, Hauswald B, Homey B, Hunzelmann N et al. Dose-response relationship of a new Timothy grass pollen allergoid in comparison to a 6-grass pollen allergoid. *Clin Exp Allergy*. 2017;47(11):1445–55.
14. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy*. 2005;60(6): 801–7.

## Author information

**Ulrike Lehnigk** has a background in human biology with a focus on immunology and pharmacology. She joined Allergopharma in 2010 working as a regulatory writer and has been a Medical Advisor since 2016.



# Pharmacovigilance for vaccines and immunotherapies: What does the medical writer need to know?

**Justina Orleans-Lindsay**

Acadustri (Medical Writing) Ltd, Camberley, United Kingdom

## Correspondence to:

Justina Orleans-Lindsay  
Acadustri (Medical Writing) Ltd  
377-399 London Road  
Camberley, Surrey  
GU15 3HL United Kingdom  
0044 (0) 1276 415 770  
Email: justina.orleans-lindsay@acadustri.com

## Abstract

Although the content of EU Periodic Benefit-Risk Evaluation Reports (PBRERs) for vaccines is governed by the same regulatory framework as applies to other medicinal products, the complex nature of vaccines presents vaccine-specific challenges that need to be considered when preparing safety documents. Notably, the complex multi-component nature of vaccines necessitates inclusion of additional data elements in vaccine PBRERs, to allow assessment of the resultant impact on the safety profile. In addition, analysis of safety data in vaccine PBRERs requires stratification of data to elucidate the impact of issues such as the effects of patient age and vaccine batch variability on the safety profile.

## Introduction

Vaccination remains one of the most effective public health measures, with well documented benefits for the individual patient and community. Vaccination triumphs include the eradication of infectious diseases such as smallpox in addition to more recent and exciting developments such as the human papillomavirus vaccination programmes for adolescent girls and the rapidly advancing area of therapeutic vaccines as used for the immunotherapy of cancer. Like all medicinal products, the use of vaccines is not without safety concerns and requires stringent processes to ensure continuous surveillance of quality, efficacy, and safety. The pharmacovigilance of vaccines was defined by a Council for International Organizations of Medical Sciences (CIOMS)/WHO working group as the “science and activities related to the detection, assessment, understanding and communication of adverse events following immunisation and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation”.<sup>1</sup> Although pharmacovigilance processes for vaccines are similar to those applied to other medicinal products, there are a number of vaccine-specific aspects that the pharmacovigilance medical writer should

consider when preparing safety documents such as the Periodic Benefit-Risk Evaluation Report (PBRER).

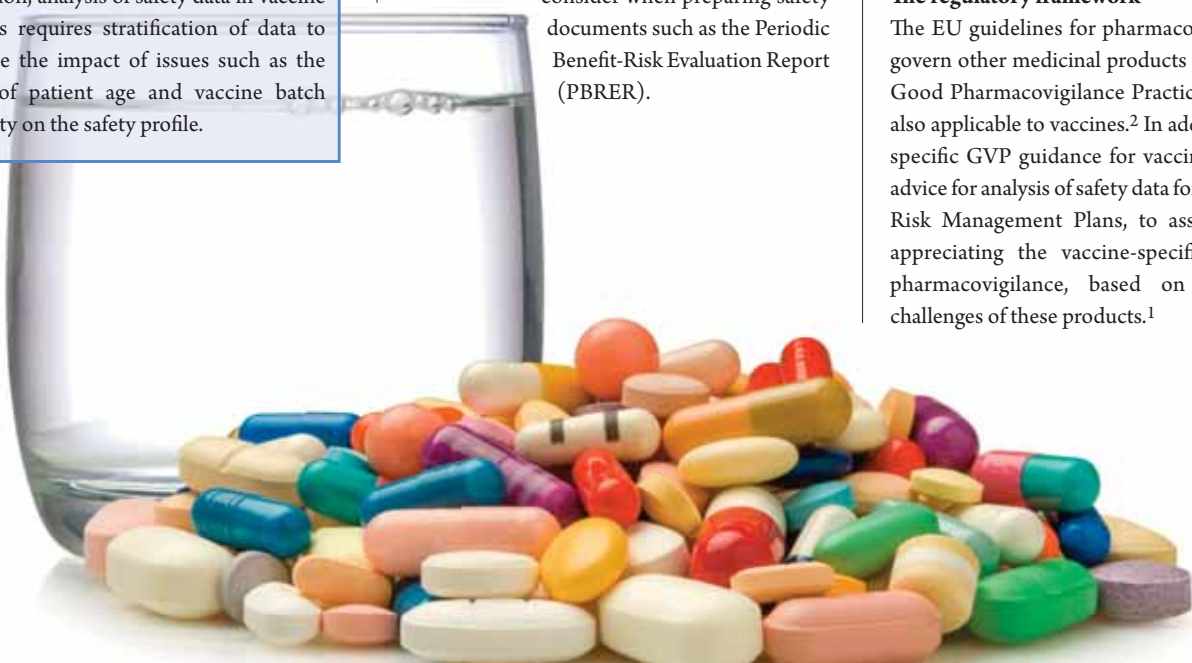
## PBRERs for prophylactic/preventative vaccines

Vaccines are complex biological products that may include multiple antigens, live organisms, adjuvants, and preservatives. These components all have potential implications for safety and require specific manufacturing processes underpinned by constantly evolving technology. Consequently, vaccines require specific pharmacovigilance systems and present many challenges that have implications for the analysis of the safety data in PBRERs, including the following:

- The need to ensure efficient handling and assessment of a high volume of suspected adverse reactions, which can be reported to the marketing authorisation holder (MAH) in a short period of time during mass vaccination programmes.
- The need to ensure real-time signal assessment during mass vaccination programmes to allow for timely identification of potential new risks. This is of specific importance for prophylactic vaccines against infectious diseases, as they are administered to an otherwise healthy population and therefore the acceptable level of risk is lower than for other medicinal products.<sup>1</sup>

## The regulatory framework

The EU guidelines for pharmacovigilance that govern other medicinal products in the form of Good Pharmacovigilance Practices (GVP) are also applicable to vaccines.<sup>2</sup> In addition, there is specific GVP guidance for vaccines, including advice for analysis of safety data for PBRERs and Risk Management Plans, to assist MAHs in appreciating the vaccine-specific aspects of pharmacovigilance, based on the unique challenges of these products.<sup>1</sup>



The additional GVP guidance on vaccines intended for prophylaxis against infectious diseases advises that reports of vaccination failures be reported as lack of therapeutic efficacy within 15 days of the MAH becoming aware of them, as they represent potential signals of reduced immunogenicity in the patient population, declining immunity, or loss of coverage for the target antigen(s). The concept of signals for vaccines is consistent with the definition as applied to other medicinal products (i.e., information pointing to a new potentially causal relationship between a medicinal product and an adverse effect, or a new characteristic of a documented relationship). However, unlike for other medicinal products, data suggestive of reduced efficacy, vaccine failures, and changes to product quality could also constitute a safety signal for vaccines. For these reasons, vaccine pharmacovigilance requires extremely detailed post-marketing surveillance data, to ensure that information pertaining to the specific vaccine batch administered to each patient is recorded in the case reports entered into the MAH's safety database.<sup>1</sup>

Compared to review of safety data for other medicinal products, there are also some other notable differences in the assessment of vaccine safety data, with five possible designated categories used for the review of adverse events following immunisation:<sup>3</sup>

- vaccine product-related
- vaccine quality defect-related
- immunisation error-related
- immunisation anxiety-related
- coincidental event

In the review of safety data for vaccine PBRERs, these five categories support the analysis of root causes for the reported adverse events, thereby enabling the MAH to further refine the applicable risk minimisation measures.

#### Additional data for presentation in vaccine PBRERs

In line with other authorised medicinal products, the content of EU PBRERs for vaccines is governed by GVP Module VII (Revision 1) and ICH E2C (R2).<sup>4,5</sup> However, there are additional considerations for vaccine PBRERs. In the first instance, there are additional data elements for inclusion in vaccine PBRERs, as outlined in Figure 1.

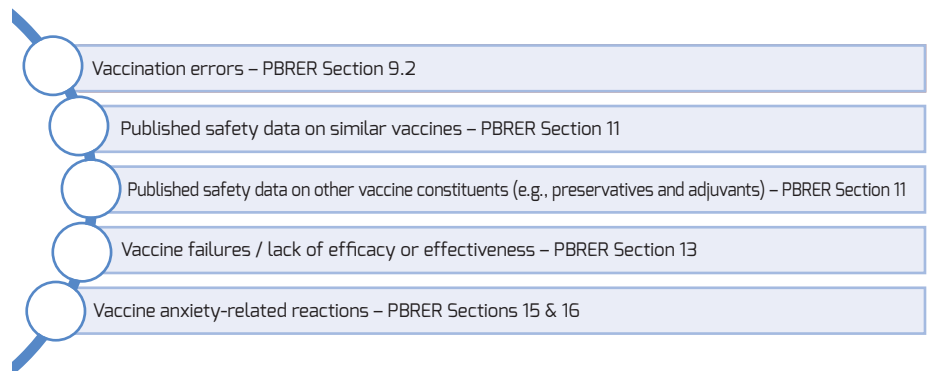


Figure 1. Additional data elements for presentation in the vaccine Periodic Benefit-Risk Evaluation Reports (PBRER)

#### Vaccination errors

In the same way that medication errors are reviewed in Section 9.2 of the EU PBRER for other medicinal products, vaccine PBRERs require analysis of any data pertinent to vaccination errors, which may include case reports describing inappropriate methods of vaccine administration (e.g., use of the incorrect route of administration, administration of insufficient doses, and failure to use the authorised diluent) or failure to comply with the authorised vaccination schedule. Review of such vaccination errors needs to include information on the cause of the error (e.g., confusion regarding the product labelling or multiple vaccination programmes leading to too many administrations), when available, and an assessment of the associated clinical consequences (which may include the onset of specific adverse events or vaccination failure).

In addition to vaccination errors occurring due to inappropriate administration of the vaccine, Section 9.2 of vaccine PBRERs should also include assessment of any reports describing improper handling and/or storage of the product, as such issues could lead to adverse effects consequent to contamination of the vaccine product with bacterial or other potentially infectious agents.

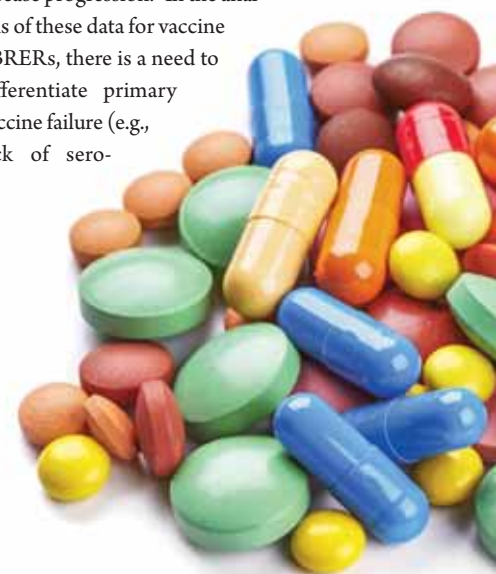
#### Published data

Section 11 of the EU PBRER for other medicinal products requires analysis of any new and significant safety information from published literature. The same requirement is applicable to vaccines and also extends to the need for inclusion of published data relevant to other

products of the same class. However, vaccine PBRERs go a step further in requiring review of published information pertinent to other vaccine constituents, such as preservatives, stabilisers, and adjuvants. Therefore, search and review criteria used for published literature for inclusion in vaccine PBRERs need to be designed to account for this difference in requirements for vaccine PBRERs.

#### Vaccine failures/lack of efficacy or effectiveness

For other medicinal products developed for the treatment or prevention of serious or life-threatening illnesses, Section 13 of the EU PBRER requires analysis of controlled clinical data that are indicative of lack of efficacy or diminished efficacy when compared to established therapies for the target disease.<sup>4</sup> Similarly, vaccine PBRERs require analysis of any case reports describing vaccine failures, which are determined based on clinical endpoints or immunological parameters used to monitor disease progression.<sup>3</sup> In the analysis of these data for vaccine PBRERs, there is a need to differentiate primary vaccine failure (e.g., lack of sero-

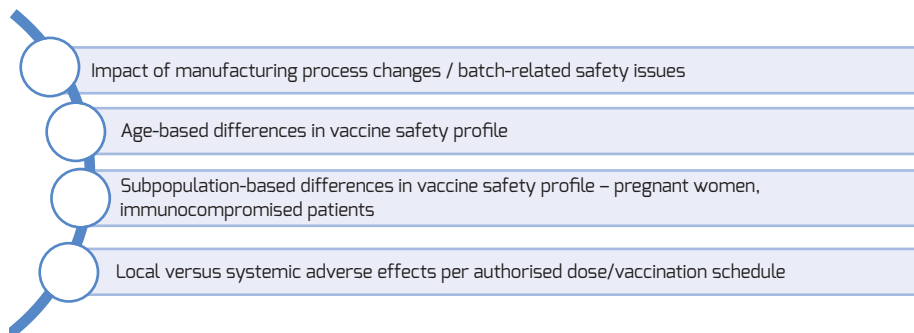
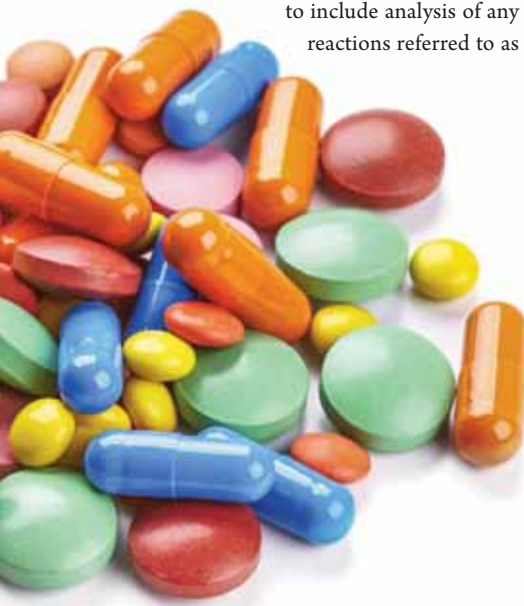


conversion or seroprotection) from secondary vaccine failure (e.g., declining immunity after an otherwise successful vaccination).

In addition, analysis of data for vaccine PBRERs should also determine the reason for the vaccination failure, which could be attributed to actual “vaccine failure” or “failure to vaccinate” (e.g., administration errors leading to an inadequate dose or lack of recommended booster vaccinations). The failure-to-vaccinate scenario involves inappropriate administration of the vaccine and therefore the ensuing analysis should be linked by appropriate cross-references to the analysis of vaccination errors as presented in PBRER Section 9.2. Analysis of vaccine failure data in the PBRER should further aim to determine whether the failure was “vaccinee-related” or “vaccine-related”. Vaccinee-related failures may be linked to the patient’s health status and may include issues such as pre-existing infections, immunodeficiency, immunosuppression, and age-related decline in immune responsiveness. In contrast, vaccine-related failures indicate lack of vaccine effectiveness against the target antigen, which may be associated with manufacturing issues or insufficient coverage (or loss of coverage) against the organism(s) responsible for the target disease.

**Vaccine anxiety-related reactions**

For other medicinal products, Section 15 of the EU PBRER should include an analysis of data pertaining to topics of special interest and any analyses specifically requested by regulatory authorities,<sup>6</sup> and Section 16 should include further analysis of signals and important risks.<sup>4,5</sup> In the vaccine setting, this requirement extends to include analysis of any reactions referred to as



**Figure 2. Additional considerations for data analysis in the vaccine Periodic Benefit-Risk Evaluation Reports**

“vaccine or immunisation anxiety-related reactions”, such as vasovagal syncope, hyperventilation-mediated reactions, and stress-related psychiatric disorders.<sup>3</sup> In addition, consideration should be given to the analysis of adverse events associated with co-administration of the vaccine with other vaccines, and the consequent implications for safety should be reviewed.

**Additional considerations for data analysis in vaccine PBRERs**

After consideration of the additional data for inclusion in EU PBRERs for vaccines, there are also numerous other factors that affect the manner in which safety data are analysed, as outlined in Figure 2.

**Impact of manufacturing changes/ batch-related safety issues**

Assessment of safety data for vaccine PBRERs relies on the understanding that, in contrast to other medicinal products, vaccines tend to be multi-component products prepared using complex biological systems that are constantly evolving due to technological advances, but which are also subject to more variability dependent on differences in manufacturing sites. These factors can have an inherent impact on the safety profile of the vaccine product, due to batch variability. Therefore, batch analyses may need to be included within the safety reviews of vaccine PBRERs.

**Age-based differences in vaccine safety profile**

Since immunological responses to vaccines evolve with age, the analysis of safety and efficacy data for vaccine PBRERs should be stratified by patient age groups, to support the identification of risks that may be more prevalent in a specific

age group. Stratification of vaccine safety data analysis by age group can also permit enhanced assessment of causality, particularly for adverse events concerning children, as it can provide a rationale for the exclusion of clusters of adverse events that may be coincidental (i.e., unrelated to vaccine exposure), if they are known to occur at a specific time during childhood. To support analysis and presentation of vaccine safety data stratified by age in vaccine PBRERs, it is worth also presenting an analysis of patient exposure data with stratification by age; however, achieving such data stratification requires high quality post-marketing surveillance data.

**Subpopulation-based differences in vaccine safety profile**

As with age, analysis of safety data in vaccine PBRERs should also be stratified by patient subpopulations, which can include pregnant women and immunosuppressed or immunocompromised patients.

**Local versus systemic adverse effects**

Another consideration for data analysis in vaccine PBRERs is the review of data to characterise the product’s safety profile with respect to the potential for local versus systemic adverse reactions. This is of particular significance in that it supports MAH refinement of the selected risk minimisation measures.

**A word on the benefit-risk assessment**

The integrated benefit-risk assessment undertaken for EU PBRERs for other medicinal products remains a contentious issue for many MAHs, with ongoing debates on the methods used to assess benefit-risk and the respective merits of qualitative or quantitative approaches.

Naturally, these issues remain relevant for vaccine PBRERs, but, as one would expect given the nature of these products, there are additional vaccine-specific factors that bring more complexity to integrated benefit-risk assessments for vaccine PBRERs:

- Prophylactic vaccines for infectious diseases are usually administered to an otherwise healthy population, including very young children and vulnerable people, and therefore the acceptable level of risk is very low compared to medicines intended for serious illnesses such as cancer. It is worth mentioning that, rightly or wrongly, this low acceptance of risk is often driven by public perceptions. That notwithstanding, benefit-risk assessments for vaccine PBRERs need to consider the clinical consequences of contracting the vaccine-preventable diseases.
- Based on the low acceptable level of risk, rare and non-serious events that may not have a significant impact on benefit-risk assessment for other medicinal products can have a profound impact in the vaccine setting and are therefore reviewed with greater scrutiny in vaccine PBRERs.
- In stark contrast to many other medicinal products, one could consider that there is no such thing as an “established safety profile” in the vaccine setting, as the safety profile is liable to change over time due to vaccine product variability based on the manufacturing process, in addition to potential changes in strains of the organism(s) behind the target disease, which may also be affected by seasonal or geographical differences. This has significant implications for the integrated benefit-risk assessment undertaken in EU PBRERs, as the benefit-risk balance is more dynamic and changeable than that for many other medicinal products.

## Conclusions

Although governed by the same regulatory expectations as other medicinal products, preparation of the EU PBRER for vaccines requires the inclusion of additional elements, to account for the more complex nature of these products and the resultant potential impact on the safety profile. Furthermore, the analysis of safety data in vaccine PBRERs is enhanced by stratification of data to elucidate the potential impact of age, product batches, and patient subpopulations on the safety profile.

## Acknowledgements

The author would like to thank Dr Chrysi Petraki for her assistance with the preparation of this article.

## Conflicts of Interest

The author is the owner/founder of Acadustri (Medical Writing) Ltd.

## References

1. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases. European Medicines Agency. 2013 [cited 2017 Dec 21]. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/12/WC500157839.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/12/WC500157839.pdf).
2. Guidelines on good pharmacovigilance practices (GVP). European Medicines Agency. 2017 [cited 2017 Dec 21]. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2017/10/WC500236404.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/10/WC500236404.pdf).
3. Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Council for International Organizations of Medical Sciences (CIOMS). 2012 [cited 2017 Dec 21]. Available from: [http://www.who.int/vaccine\\_safety/initiative/tools/CIOMS\\_report\\_WG\\_vaccine.pdf](http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf).
4. Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1). European Medicines Agency. 2013 [cited 2017 Dec 21]. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientificguideline/2013/04/WC500142468.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientificguideline/2013/04/WC500142468.pdf).
5. ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER). 2013 [cited 2017 Dec 21]. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2012/12/WC500136402.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/12/WC500136402.pdf).
6. E2C(R2) Implementation Working Group ICH E2C(R2) Guideline: Periodic Benefit-Risk Evaluation Report Questions & Answers. 2014 [cited 2017 Dec 21]. Available from: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E2C/E2C\\_R2\\_QAs\\_Step4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_QAs_Step4.pdf).

## Author Information

Dr Justina Orleans-Lindsay is the owner/founder of Acadustri (Medical Writing) Ltd, which provides specialist pharmacovigilance medical writing services to the pharmaceutical industry. Dr Orleans-Lindsay is also a visiting lecturer at the University of Hertfordshire, where she supports the postgraduate programme in pharmacovigilance.



# Addressing vaccine hesitancy in writing

**Michelle Guillemard**

Health Writer Hub, Sydney, Australia

## Correspondence to:

Michelle Guillemard  
editor@healthwriterhub.com

## Abstract

Since the infamous article by Wakefield et al. was published in 1998, diseases once nearly eradicated are re-emerging. As a result, research has focused on communication strategies that can successfully combat vaccine hesitancy. Current research suggests that facts and knowledge alone are not sufficient to change the minds of people hesitant to use vaccines. Strategies that might help “anti-vaxxers” to reconsider include approaching vaccine hesitancy as a spectrum of opinions, communicating with courtesy, focusing on the harms of not vaccinating, using narrative in communications, and analysing real-life stories from former vaccine-hesitant parents.

Had *The Lancet* not published their now-retracted article, “Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children” by Andrew Wakefield et al. in 1998,<sup>1</sup> perhaps we wouldn’t be

facing one of the most significant public health challenges of our time. Had they never written the words “Rubella virus is associated with autism and the combined measles, mumps, and rubella vaccine, (rather than the monovalent measles vaccine), has also been implicated”, perhaps we wouldn’t be witnessing the re-emergence of diseases that were once eradicated.<sup>2</sup> But, they did – and, we are.

If you’ve ever seen or participated in an online discussion about vaccination, you’ll appreciate just how difficult it is to change an anti-vaxxer’s mind. Vaccination is a hot topic on social media – specifically, in online parenting groups where many mothers refer to the issue as a “debate” with two “equal sides”, dismissing the science and facts by arguing that people are entitled to their opinion.

Defensive mothers cite material with no evidence base to support their claim that the MMR vaccine is harmful and causes autism. Discussion threads on vaccination often become so heated that many moderators ban all discussion on the topic – another challenge in the fight against the anti-vaccination movement, as pro-vax silence makes the anti-vaccination voice louder.

## Tackling vaccine hesitancy in writing

As medical writers, we’re public health advocates. It’s our job, our obligation, to write high-quality content and correct misinformation. As logical

thinkers, we believe the best way to counter anti-vaccination voices is to offer up evidence and knowledge. We wrongly assume people don’t want to vaccinate simply because they don’t know the facts. All we need to do is bust the myths and debunk the pseudoscience, right? Wrong.

In 2013, Dube et al. explored the issue of vaccine hesitancy, writing in the journal *Human Vaccines & Immunotherapeutics*.<sup>3</sup> The team wrote that “public health interventions to promote vaccination have been based on a ‘knowledge-deficit’ approach assuming that vaccine hesitant individuals would change their mind if given the proper information.” However, the authors argued, research on vaccine acceptance has shown a different result. “Individual decision-making regarding vaccination is far more complex and may involve emotional, cultural, social, spiritual or political factors as much as cognitive factors,” they wrote.

Five years later, the issue of vaccine hesitancy remains as critical as ever and the same journal published another paper on the topic – this time looking at addressing barriers to vaccine acceptance.<sup>4</sup> “Overcoming hesitancy requires detection, diagnosis and tailored intervention as there is no simple strategy that can address all of the barriers to vaccine acceptance,” the authors wrote. While Europe has a relatively



Andrew Wakefield

## The MMR vaccine controversy

In 1998, *The Lancet* published a study linking the combined measles, mumps, and rubella (MMR) vaccine to colitis and autism spectrum disorders.<sup>1</sup> Authored by a group led by Andrew Wakefield, the study received significant media attention and vaccination results began to drop as frightened parents refused to vaccinate their children.<sup>16</sup> Further research failed to replicate the findings,<sup>17</sup> Wakefield was investigated for professional misconduct and subsequently banned from practicing medicine,<sup>18</sup> and *The Lancet* formally retracted the paper in 2010, arguing that the science was flawed. Yet the damage was well and truly done: The paper has become a significant tool used by the anti-vaccination movement to convince hesitant parents not to vaccinate their children, and Wakefield’s study continues to have a considerable impact on public health.

high vaccine uptake, there are pockets of resistance<sup>5</sup> and researchers argue we mustn't become complacent. And, with most parents getting their health information online, it's critical we arm ourselves with best-practice techniques so that, when opportunity arises, we can help to make a difference. So, if knowledge, facts and evidence don't help to address vaccine hesitancy, what does? Here are some strategies that have shown success in positively changing people's attitudes on vaccination.

### Understand the vaccine hesitancy

Whether you're writing a consumer article about vaccination or contributing to an online discussion, it's important to understand the anti-vaccination mind-set. Simply put, not all anti-vaxxers are the same. Writing in *The Conversation* last year, Australian researchers argued that vaccine attitudes are not simply "pro" or "anti."<sup>6</sup> Instead, they said, there's a "spectrum" of vaccine hesitancy – one that parents move through, not necessarily sequentially. Depending on where people are at on the spectrum, different information will resonate in different ways.

"Our research, and that of others, suggests parents' confidence in the safety and need for vaccination is best described as a spectrum,

ranging through unquestioning acceptance; cautious acceptance; hesitance; delaying or selective vaccinators; to those who decline all vaccines. Within that group of decliners, only a handful are the noisy 'anti-vaccination' activists," the authors wrote. The team also pointed out that it's the hesitant parents who are most likely to change their positions because they can be reassured.

### Direct attention to the consequences of not vaccinating

Instead of writing about the reasons why vaccination is helpful, focus on the dangers of refusal – that's one strategy that has proven to be effective, according to American researchers. A research team from the University of Illinois found they could moderate anti-vaccination beliefs by reminding people of the harms that not vaccinating can have.<sup>7,8</sup> Fear can be a strong motivator for change, and that strategy has worked in other public health interventions – for example, cigarette label imagery.


### Communicate with courtesy

"Communication is a two-way process," wrote members of the SAGE Working Group on Vaccine Hesitancy in the journal *Vaccine*.<sup>9</sup> "It is in equal measure a process of listening and telling." "Understanding the perspectives of the people for whom immunisation services are intended, and their engagement with the issue, is as important as the information that experts want to communicate." Too often, pro-vax arguments direct vitriol, passive aggressiveness and hate speech at anti-vaxxers. This negativity only creates a further divide. When you're communicating with someone who is anti-vaccination, it is important to:

- Acknowledge the other person's belief or mind-set – acknowledgement doesn't mean you agree with them
- Communicate with empathy – listen, then share your perspective
- Use the right tone – different tones resonate with different audiences

Other communication strategies that can help to change an anti-vax mind-set, according to a team of doctors writing for *Medscape*,<sup>10</sup> are to:

- Reinforce the importance of the decision
- Ask what types of blogs and content are influencing their decision-making



As medical writers, we're public health advocates. It's our job, our obligation, to write high-quality content and correct misinformation.

- Understand the source of the reader's fears
- Explain the risks of not vaccinating
- Explicitly mention and acknowledge the fact that your reader is a caring parent who is trying to make the best decisions for the health of her child

Making someone feel valued and good isn't just common courtesy, either – it's also an evidence-based approach to changing misperceptions. A research team looking at misperceptions and corrections found that people who undertook a self-affirmation exercise were more likely to accept corrected information.<sup>11</sup>

Further, in 2016, the WHO developed an evidence-based guideline, *How to respond to vocal vaccine deniers in public*.<sup>12</sup> In the guideline, WHO also recommend the following communication strategies:

- Stay calm
- Don't demean the anti-vaxxer
- Focus on the category of the anti-vax argument – is the topic about safety, fear, etc.?
- Provide the evidence with respect
- Use appealing language



## Narrative

Emotion is a powerful motivator, and it is personal stories, not facts, that engage readers. Once those stories become about multiple people, we lose interest. As explained by Christopher Graves in *Harvard Business Review*, “It turns out human empathy does not scale well. We can care very deeply about one, single stranger, but that empathy wanes rapidly as the group of victims grows. Once it becomes a large number we cease caring.”<sup>13</sup> Graves tells how celebrity anti-vax campaigner Jenny McCarthy used her personal experience with her child to sway audiences into believing her anti-vaccination story, playing the role of identifiable victim.

## Consider real-life stories

Reading real-life stories from people who have changed their minds also helps to provide an insight into the anti-vaccination mind-set – and how it was successfully changed.<sup>14</sup> In many cases, these stories tell of people who came into the

anti-vax movement via friends with similar parenting styles in other areas, suggesting the significance of peer support. Clearly, we naturally gravitate towards people who have similar thoughts and values to our own. One mother who shared her story on Australian website Kidspot confessed: “I no longer am an anti-vaxxer. You may wonder what changed my mind. I’ll tell you what didn’t first: being confronted with new evidence that opposed my views didn’t change my mind, and neither did the scorn and derision of people who disagreed with my choice,

With most parents getting their health information online, it’s critical we arm ourselves with best-practice techniques so that, when opportunity arises, we can help to make a difference.

in real life or online.”<sup>15</sup>

Instead, the mother argued, her mind-set shifted after reading posts from a pro-vaccination friend with similar parenting styles. “Every interaction [my friend] had on the topic was friendly, non-confrontational and respectful, and yet she thoroughly explained her reasoning for vaccinating and gently challenged any misconceptions she saw in vaccine opponent’s arguments,” the author wrote. “And so I read articles she posted, and followed her links to accurate information from reputable sources.” Gentle persuasion slowly allowed this anti-vaxxer to challenge her deeply held beliefs.

## The final word

While correcting misinformation is an important step in the journey, it cannot be the only way forward. Science seems to demonstrate that a multi-faceted, individualised and contextualised approach is the best way to make an impact against the anti-vaccination movement.



Instead of writing about the reasons why vaccination is helpful, focus on the dangers of refusal – that’s one strategy that has proven to be effective, according to American researchers.

## References

1. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*. 1998;351:637–41.
2. Sifferlin A. 4 diseases making a comeback thanks to anti-vaxxers. 2014 [cited 2018 Jan 24]. Available from: <http://time.com/27308/4-diseases-making-a-comeback-thanks-to-anti-vaxxers/>.
3. Dube E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J. Vaccine hesitancy: an overview. *Hum Vaccin Immunother*. 2013;9:1763–73.
4. MacDonald NE, Butler R, Dube E. Addressing barriers to vaccine acceptance: an overview. *Hum Vaccin Immunother*. 2018;14:218–24.
5. Vanderslott S. Despite scepticism, Europe has high vaccination rates – but it shouldn’t be complacent 2017 [cited 2018 Jan 24]. Available from: <https://theconversation.com/despite-scepticism-europe-has-high-vaccination-rates-but-it-shouldnt-be-complacent-75169>.
6. Leask J, Danchin M, Berry NJ. Australians’ attitudes to vaccination are more complex than a simple ‘pro’ or ‘anti’ label. 2017 [cited 2018 Jan 24]. Available from: <https://theconversation.com/australians-attitudes-to-vaccination-are-more-complex-than-a-simple-pro-or-anti-label-74245>.
7. Horne Z, Powell D, Hummel JE, Holyoak KJ. Countering antivaccination attitudes. *Proc Natl Acad Sci U S A*. 2015;112:10321–4.
8. Collins N. Changing Anti-vaxxers’ minds. 2015 [cited 2018 Jan 24]. Available from: <https://psmag.com/social-justice/changing-anti-vaccine-minds>.
9. Goldstein S, MacDonald NE, Guirguis S. Health communication and vaccine hesitancy. *Vaccine*. 2015;33:4212–4.
10. Poland GA, Poland CM. Changing minds about vaccination. 2015 [cited 2018 Jan 24]. Available from: <https://www.medscape.com/viewarticle/839980>.
11. Nyhan B, Reifler J. The roles of information deficits and identity threat in the prevalence of misperceptions. Hanover (NH): Dartmouth College, 2017.
12. WHO Regional Office for Europe. How to respond to vocal vaccine deniers in public. Geneva: WHO, 2016.
13. Graves C. Why debunking myths about vaccines hasn’t convinced dubious parents. 2015 [cited 2018 Jan 24]. Available from: <https://hbr.org/2015/02/why-debunking-myths-about-vaccines-hasnt-convinced-dubious-parents>.
14. Calise L. A visceral, overwhelming empathy. 2016 [cited 2018 Jan 24]. Available from: <https://www.voicesforvaccines.org/a-visceral-overwhelming-empathy/>.
15. Vigeant C. I was a proud anti vaxxer. Here’s what changed my mind. 2017 [cited 2018 Jan 24]. Available from: <http://www.kidspot.com.au/parenting/real-life/reader-stories/i-was-a-proud-anti-vaxxer-heres-what-changed-my-mind/news-story/e542f8dc2f26e3a0ca21321cc10eac7b>.
16. Smith R. MMR uptake rates finally recovered from Wakefield scandal figures show. *The Telegraph*. 2012 Nov 27. [cited 2018 Jan 24]. Available from: <http://www.telegraph.co.uk/news/health/news/9705374/MMR-uptake-rates-finally-recovered-from-Wakefield-scandal-figures-show.html>.
17. Global Advisory Committee on Vaccine Safety. MMR and autism. 2003 [cited 2018 Jan 24]. Available from: [http://www.who.int/vaccine\\_safety/committee/topics/mmr/mmr\\_autism/en/](http://www.who.int/vaccine_safety/committee/topics/mmr/mmr_autism/en/).
18. Deer B. How the case against the MMR vaccine was fixed. *BMJ*. 2011;342:c5347.

## Author information

**Michelle Guillemard** is the President of the Australasian Medical Writers Association and the Founder of Health Writer Hub, an eLearning platform for health writers. Michelle is passionate about creating better health outcomes through evidence-based communication and believes high-quality health writing has the power to improve global health standards and change lives.

# Results of the 2017 EMWA salary survey

Ansgar Dressler,<sup>1</sup> Julia Forjanic Klapproth,<sup>1</sup>  
and Andrea Rossi<sup>2</sup>

1 Trilogy Writing & Consulting, GmbH,  
Frankfurt, Germany

2 Eli Lilly & Co., Sesto Fiorentino, Italy

## Correspondence to:

Julia Forjanic Klapproth  
Trilogy Writing & Consulting, GmbH  
Falkensteiner Strasse 77  
60322 Frankfurt, Germany  
+49 69 138 2528 11  
julia@trilogywritting.com

## Abstract

Between April 7 and May 31, 2017, EMWA members were asked to participate in a survey about their current salary levels. 317 individuals responded, of whom 266 (84%) were evaluable (191 employees and 75 freelancers). Most respondents were women (77%), and most lived in the United Kingdom (30%) or Germany (27%). Most worked as freelancers (28%), for a pharmaceutical company (22%), or for a contract research organization (CRO) (22%). About half had ≤5 years of writing experience. For employed medical writers, the mean annual income was €62,793 (median €58,000). For freelance medical writers, the mean hourly income was €81 (median €80). On average, income for employed medical writers was similar for men

and women and rose with work experience and responsibility. However, for freelance medical writers, the average hourly income was significantly higher for men (€102) than for women (€75). Highest academic degree and geographical location influenced income for employed medical writers but had less impact for freelancers. Both employed and freelance members with an EMWA Professional Development Programme certificate earned more than those without. The results suggest that the income of employed medical writers depends primarily on the type of company and the amount of work experience and training as a medical writer. For freelancers, income appears to depend mostly on the amount of writing experience and training they have.



## Introduction

EMWA conducted its first salary survey in 2006 to which 145 employed EMWA members responded.<sup>1</sup> The survey was repeated in 2012, with 320 members responding.<sup>2</sup> A third survey was conducted in 2017 and is reported here. Although separate surveys were previously conducted for freelance medical writers (including 63 freelancers in 2003, 101 in 2007, 130 in 2010, and 123 in 2013),<sup>3–6</sup> the current survey included both freelancers and employed medical writers, which allows for comparison of incomes and patterns between these 2 groups.

## Methods

### Survey details

The present survey was based on the previous questionnaires, although a few questions relevant to understanding the salary level (e.g. whether a person has supervisory responsibilities or not) were added and the survey was adapted to allow freelancers to participate. The questions included in the survey are summarised in the Appendix. The survey was set up and administered online via Survey Monkey (<http://www.surveymonkey.com>). EMWA members were invited to participate via email, social media, and announcements on the EMWA website and in *Medical Writing*. A reminder was sent to all invitees shortly before the end of the survey period. The survey was open for participation from April 7 to May 31, 2017. All answers were collected and kept strictly confidential. As the survey was anonymous, it was not possible to query missing or inconsistent data.

### Statistical analyses

For the purpose of assessing income, the respondents were divided into two full analysis sets (FAS) based on whether they were employees (the employee FAS) or freelance (the freelance FAS). The employee FAS consisted of all respondents who selected employer type as anything except “I am a Freelance” and job title as anything except “Freelance” and who provided information for annual salary. The freelance FAS consisted of all respondents who selected employer type as “I am a Freelance” or job title as “Freelance” and who provided an hourly rate. When respondents provided both hourly and annual income, they were assigned to the freelance FAS or employee FAS according to their answer to employer type. Respondents missing any of this information or who did not

comply with these rules were excluded from the analyses. The combination of these two FAS comprised the total FAS.

Data on demographics, background, and job characteristics were summarised for each FAS (total, employee, and freelance). Means, standard deviations (SD), medians, and ranges were reported for income data (annual salaries and hourly rates). Simple analysis of covariance models were used to assess the impact of each explanatory variable on the annual income/hourly rate.

The annual income reported by a few freelancers was removed so that freelance incomes were only assessed based on hourly rates.

Missing values were not replaced. Pounds were converted to Euros using official exchange rates on 16 June 2017, where 1 £ = 1.14237326 €.

## Results

### Respondent characteristics

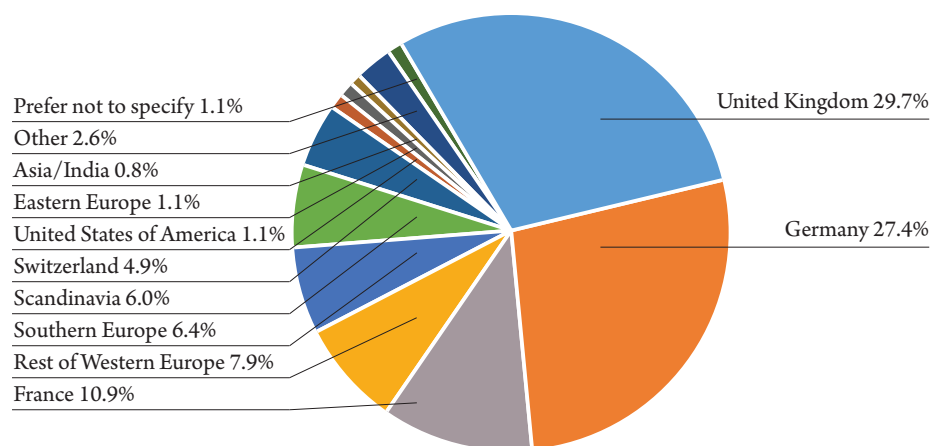
A total of 317 EMWA members responded to the survey of whom 221 (70%) were employees, 89 (28%) were freelance, and 7 (2%) did not classify their employment situation. The employee FAS comprised 191 respondents, and the freelance FAS comprised 75 respondents.

The majority of respondents in the total FAS were women (77%), and most lived in the UK (30%) or Germany (27%) (Table 1; Figure 1). Proportions were similar in the employee FAS

and freelance FAS. Among the employee FAS, 16% worked part-time (all but one of whom were women) compared to 48% among the freelance FAS (all but three of whom were women). In the total FAS, approximately one third of respondents (35%) worked an average of >40 h/week; however, this proportion was much higher among employed writers (41%) than among freelancers (17%).

The academic background, level of training, and average time in the industry were similar among employed and freelance writers. In the total FAS, most respondents had an advanced academic degree (master’s degree or higher, 89%), and the most common fields of study had been biological and other life sciences and healthcare (86%). Only 32% had already obtained an EMWA professional development programme (EPDP) certificate, and 93% had not completed any other formal training or certification in medical writing (e.g. certificate from the American Medical Writers Association or the Drug Information Association). The majority of respondents had been working in the pharmaceutical industry for >5 years (78%), but half (50%) had ≤5 years of experience as a medical writer (Table 1).

Among employed medical writers, most worked for either a pharmaceutical company (31%), a contract research organisation (CRO) (31%), or a company offering medical writing



**Figure 1. Geographical location of medical writers (Total FAS population)**

Any country with fewer than 5% of total respondents was grouped by region as follows: Asia/India (China, Hong Kong, India, Japan, Singapore, Thailand), Eastern Europe (Czech Republic, Lithuania, Poland, Romania, Russian Federation, Serbia), Rest of Western Europe (Austria, Belgium, Ireland, The Netherlands), Rest of World (Turkey, Israel, other), Scandinavia (Denmark, Finland, Sweden), and Southern Europe (Greece, Italy, Spain, Portugal).

Table 1. Demographic and work-life characteristics

Characteristic	Number (%) of respondents		
	Employee FAS	Freelance FAS	Total FAS
Total	191 (100)	75 (100)	266 (100)
Women	148 (77) <sup>a</sup>	56 (75) <sup>a</sup>	204 (77) <sup>a</sup>
Country working in			
UK	57 (30)	22 (29)	79 (30)
Germany	54 (28)	19 (25)	73 (27)
France	20 (10)	9 (12)	29 (11)
Scandinavia (Denmark, Finland, Sweden)	10 (5)	6 (8)	16 (6)
Switzerland	12 (6)	1 (1)	13 (5)
Spain	6 (3)	3 (4)	9 (3)
Belgium	6 (3)	2 (3)	8 (3)
Austria	6 (3)	–	6 (2)
Italy	5 (3)	1 (1)	6 (2)
Other	15 (8)	12 (16)	27 (10)
Full-time employment	160 (84)	39 (52)	199 (75)
Hours worked per week			
1–10	0	5 (7)	5 (2)
11–20	2 (1)	8 (11)	10 (4)
21–30	15 (8)	18 (24)	33 (12)
31–35	17 (9)	15 (20)	32 (12)
36–40	78 (41)	16 (21)	94 (35)
>40	79 (41)	13 (17)	92 (35)
Time working as medical writer			
≤5 years	102 (53)	30 (40)	132 (50)
>5 years	89 (47)	45 (60)	134 (50)
Employer type			
Contract research organisation	59 (31)	–	59 (22)
Pharmaceutical company	59 (31)	–	59 (22)
Medical writing company	41 (21)	–	41 (15)
Communications/advertising agency	10 (5)	–	10 (4)
Biotech company	7 (4)	–	7 (3)
Other	15 (8)	–	15 (6)
Freelance	–	75 (100)	75 (28)
Supervisory responsibility <sup>b</sup>			
Line management	42 (22)	7 (9)	49 (18)

FAS: full analysis set

<sup>a</sup> 5 respondents in the FAS populations (3 employees and 2 freelancers) preferred not to reveal their gender.

<sup>b</sup> Oversight of a project but not line management.

services (21%) (Table 1). Although the majority of employed writers worked for medium-sized (50–1000 people; 40%) or large companies (>1,000 people; 37%), almost one quarter (23%) worked for small companies (<50 people).

While both employed and freelance writers reported having supervisory responsibilities (e.g. oversight of a project but not line management), the proportion was much higher for employed writers (Table 1). More than half of employed writers (62%) said they have supervisory responsibilities, and 22% said they have line

management activities.

Employed writers spent, on average, 45% of their working time on creating new texts based on data, 16% on editing texts that need considerable rewriting, 15% on supervision or administration (not line management), and 12% on quality control activities. On average, they also spent 33% of their time on documents for clinical and nonclinical development (clinical study protocols, clinical study reports, or statistical analysis plans), 15% on articles for scientific journals and the scientific press, and 14% on

documents for submission dossiers (Common Technical Document Module 2, Integrated Summary of Safety, or Integrated Summary of Effectiveness).

Freelance writers mostly spent their time creating new texts based on data (65% on average), followed by editing texts that need considerable rewriting (13%); the proportions of time for other predefined activities did not exceed 6%. The average percentage of time spent by freelancers was similar for documents for clinical and nonclinical development (24%) and scientific articles (25%) and less (13%) on documents for submission dossiers.

#### Gross annual income—employed medical writers

In the employee FAS, the mean gross annual income was €62,793 (SD €28,771), with a median of €58,000 (range €16,000 to €210,000). The mean income of the 40 men in the employee FAS (€63,755) was only slightly higher than that of the 148 women (€61,305), and the difference was not statistically significant.

The average starting salary of employed writers (those with ≤2 years of experience) was €45,376, which rose by approximately €15,000 for those with between 2 and 10 years of experience as a medical writer, and by another €20,000 for those with >10 years of experience (Table 2). Likewise, mean salaries also increased with more senior job titles: the lowest salary was earned by associate medical writers (€36,987) and junior medical writers (€43,637) and was highest for department heads (€109,050) (Table 3). Those respondents with supervisory responsibilities earned more (mean €69,045) than those without (€52,459), as did those with line management responsibility (€79,224) compared to those without (€58,161).

The mean salary was higher in respondents with an advanced academic degree (MBBS, MD, PhD, MBA or equivalent) (€66,265) than in those with a master's (€55,334) or bachelor degree (€55,544). Although only one third of respondents had an EPDP (EMWA Professional Development Programme) certificate, they earned more (mean €70,596) than those who did not (€59,131).

The average annual income differed considerably based on geographical location: it was highest in Switzerland (€122,417) and lowest in Austria (€47,397) (Table 4). It was also higher for writers employed at pharmaceutical

**Table 2. Gross annual income of employed medical writers by years of experience (employee FAS, N=191)**

Years working as medical writer	N (%)	Gross annual income (€)			
		Mean	SD	Median	Range
≤2 years	53 (28)	45,376	19,080	42,000	16,000–145,000
>2–5 years	49 (26)	60,145	25,334	53,500	25,000–156,000
>5–10 years	43 (23)	61,288	18,065	61,250	26,000–110,000
>10–15 years	31 (16)	88,673	35,063	70,500	55,000–210,000
>15 years	15 (8)	83,810	30,520	72,000	44,000–150,000

FAS: full analysis set; SD: standard deviation

**Table 3. Gross annual income of employed medical writers by job title (employee FAS, N=191)**

Job title	N (%)	Gross annual income (€)			
		Mean	SD	Median	Range
Associate MW	11 (6)	36,987	11,454	35,358	16,000–65,000
Junior MW	33 (17)	43,637	12,115	42,000	27,000–78,000
Senior MW	60 (31)	62,619	21,448	60,000	26,000–156,000
Principal MW	17 (9)	70,973	28,670	60,643	43,200–145,000
MW manager	22 (12)	83,168	30,931	79,500	30,000–154,000
Department head	10 (5)	109,050	47,006	101,250	58,000–210,000
Communication specialist	4 (2)	53,000	18,129	49,500	35,000–78,000
MW scientist	10 (5)	53,497	16,214	54,500	25,000–82,450
Other	23 (12)	63,287	26,351	60,000	28,559–130,000

FAS: full analysis set; MW: medical writer; SD: standard deviation

**Table 4. Gross annual income of employed medical writers by geographical location, sorted by mean income (employee FAS, N=191)**

Country of employment	N (%)	Gross annual income (€)			
		Mean	SD	Median	Range
Switzerland	12 (6)	122,417	40,673	120,000	60,000–210,000
Scandinavia	10 (5)	74,286	19,202	72,000	47,412–110,000
Germany	54 (28)	67,701	22,718	63,250	38,000–130,000
Italy	5 (3)	54,800	15,401	54,000	40,000–78,000
UK	57 (30)	53,568	22,409	47,000	26,000–150,000
Belgium	6 (3)	52,742	14,058	49,150	40,000–70,000
Spain	6 (3)	48,500	20,869	40,500	30,000–85,000
France	20 (11)	48,247	11,587	46,000	29,000–82,500
Austria	6 (3)	47,397	13,603	41,000	35,000–70,000
Other	15 (8)	62,767	32,463	64,000	16,000–145,000

FAS: full analysis set; SD: standard deviation

companies (mean €82,600) than any other company type (Table 5). The mean salaries at all other types of employer ranged from €48,902 to €57,918. The variability between minima of the salary ranges across company types was much lower than for the maxima. The maximum salaries were lowest for biotech companies and communications agencies. Mean annual salaries were also higher at larger companies (>500 employees; €70,136) than at smaller companies (€54,732). Further analyses showed that the higher incomes in these companies were from those who had worked longer (>10 years) as a medical writer.

Annual income increased with the hours worked every week: mean income was €59,162 for those who worked ≤35 h/week compared to €63,579 for those who worked >35 h/week, €68,595 for those who worked >41–50 h/week, and €95,480 for those who worked >50 h/week (Table 6).

The mean annual salary also differed with the type of document respondents primarily worked on (≥ 50% of their working time). Those who primarily worked on documents for submission dossiers (n=19) had a mean salary of €78,389, while those primarily working on documents for clinical and nonclinical development (n=64) had a mean salary of €59,406, and those primary working on scientific articles (n=28) earned mean of €48,897.

Most of the employed writers were satisfied with their work (91%) and their salary (63%). As expected, salary satisfaction correlated directly with a higher annual income: the mean salary among satisfied respondents was 28% higher (€68,286) than that of the dissatisfied respondents (€53,508) (p<0.01).

**Hourly income – freelance medical writers**

In the freelance FAS, the mean hourly income was €81 (SD €35.1), with a median of €80/hour, and a range of €15 to €200/hour. The mean hourly income of the 17 men (€102) was notably higher than that of the 56 women (€75), and the difference was statistically significant (p<0.01).

The average starting rate of freelance writers (those with ≤2 years of experience) was €56/h, which doubled to €113/h for those with between 5 and 10 years of experience as a medical writer, but was slightly less for those with >10 years of experience (Table 7). Among women, those with >10 years of experience were charging more



(mean €87/h) than those with ≤10 years of experience (€66/h), while the opposite was true for men (€111/h for ≤10 years of experience, €94/h for >10 years of experience).

Freelance rates did not differ for those with supervisory responsibilities (mean €82/h) and those without (€81/h). Unexpectedly, the few freelance writers with line management responsibility were charging less (mean €68/h) than those without (€83/h). The mean freelance rate was higher in those with a master's degree (€91/h) than those with either an advanced degree or a bachelor's degree (€79/h for both). Freelance writers who had an EPDP certificate were charging more (mean €91/h) than those who did not (€77/h).

Unlike the salaries of employed medical writers, the average hourly income did not differ much across most geographical locations: although it was higher in Scandinavia (€103/h), it was between €77 and €87/h in the other regions (Table 8).

When assessed based on average hours worked per week, mean hourly rates were slightly higher for those who worked longer: those who worked ≤35 h/week were charging an average of €74/h, whereas those who worked >35 hours/week were charging an average of €92/h.

Similar to the observation made in the employee FAS, the mean hourly rate for freelancers differed according to the type of document respondents primarily worked on (≥50% of their working time). Those who primarily worked on documents for submission dossiers (n=10) had a mean rate of €99/h, while those primarily working on documents for clinical and nonclinical development (n=20) had a rate of €87/h, and those primarily working on scientific articles (n=20) had a rate of €81/h.

Most of the freelance writers were satisfied with their work (91%) and their salary (77%). As expected, salary satisfaction correlated directly with a higher income: the mean rates were higher among satisfied respondents (€88/h) than among dissatisfied respondents (€59/h) ( $p<0.01$ ).

## Discussion

These survey results can provide a useful benchmark both for medical writers who want to assess how their current salaries compare to those of similar positions across the industry in Europe and for employers of medical writers to ensure

**Table 5. Gross annual income of employed medical writers by type of company, sorted by mean income (employee FAS, N=191)**

Type of employer	N (%)	Gross annual income (€)			
		Mean	SD	Median	Range
Pharmaceutical company	59 (31)	82,600	35,456	73,000	28,559–210,000
Communications/advertising agency	10 (5)	57,918	16,933	54,000	38,000–82,500
Contract research organisation	59 (31)	56,488	22,993	49,000	25,000–145,000
Biotech company	7 (4)	49,197	20,072	42,000	16,000–70,000
Medical writing company	41 (21)	48,902	15,356	46,000	30,000–115,000
Other <sup>a</sup>	15 (8)	57,243	16,622	58,300	34,000–89,000

FAS: full analysis set; SD: standard deviation

<sup>a</sup> Other includes research/consulting, medical device company, public sector organisation, consultancy including providing medical writing services, health technology assessment institute, governmental institution, medical communications & education agency, National Health System, consultant to the pharmaceutical industry, consulting, pharmaceutical consultancy, both freelance and employed (10 h per week), and charitable organisation

**Table 6. Gross annual income of employed medical writers by hours worked per week (employee FAS, N=191)**

Hours worked per week	N (%)	Gross annual income (€)			
		Mean	SD	Median	Range
1–20	2 (1)	71,000	1,414	71,000	70,000–72,000
21–30	15 (8)	61,615	19,465	63,000	26,000–95,000
31–35	17 (9)	55,605	22,038	46,400	29,000–110,000
36–40	78 (41)	55,051	22,486	48,500	27,000–156,000
41–50	69 (36)	68,595	34,136	60,000	16,000–210,000
>50	10 (5)	95,480	28,491	90,000	58,300–150,000

FAS: full analysis set; SD: standard deviation

**Table 7. Hourly rate of freelance medical writers according to years of experience (freelance FAS, N=75)**

Years working as medical writer	N (%)	Hourly rate (€)			
		Mean	SD	Median	Range
≤2 years	11 (15)	56	27.7	60	20–100
>2–5 years	19 (25)	67	37.0	55	15–170
>5–10 years	10 (13)	113	45.7	105	50–200
>10–15 years	13 (17)	93	31.5	80	60–160
>15 years	22 (29)	85	15.4	90	60–110

FAS: full analysis set; SD: standard deviation

**Table 8. Hourly rate of freelance medical writers according to geographical location (freelance FAS, N=75)**

Country employed	N (%)	Hourly rate (€)			
		Mean	SD	Median	Range
Scandinavia	6 (8)	103	43.7	115	50–150
France	9 (12)	87	16.0	90	60–110
Germany	19 (25)	79	32.8	80	35–170
UK	22 (29)	79	19.3	70	50–120
Other	19 (25)	77	52.0	70	15–200

FAS: full analysis set; SD: standard deviation

that the salaries being offered are competitive. With the results of this salary survey, the three surveys provide insight into salaries of medical writers in Europe over an 11-year period. With these data, we can begin to look for trends over time. Future surveys will expand the data and may strengthen the conclusions that we can draw.

The reported average salary of employed medical writers rose much more between the initial salary survey in 2006 (mean €54,924; median €50,000) and the second survey in 2012 (mean €61,505; median €54,000) than between the second survey and the current survey (mean €62,793; median €58,000).<sup>1,2</sup> This difference is certainly influenced by several factors including differences in inflation and cost of living in different European countries, differences in the number and type of EMWA members and respondent characteristics, differences in companies' working models, and, generally, differences in social and political changes across Europe.

Indeed, there was substantial geographical variability in salaries across Europe, which appears to reflect differences in cost of living, with the highest salaries in Switzerland and Scandinavia. However, since only a few medical writers responded from these countries, these averages may not reflect the true average in these regions. Because 58% of the employed medical writers resided in Germany or the UK, the average salary reported for these countries could be a good benchmark for the average income of a large proportion of employed medical writers across Europe.

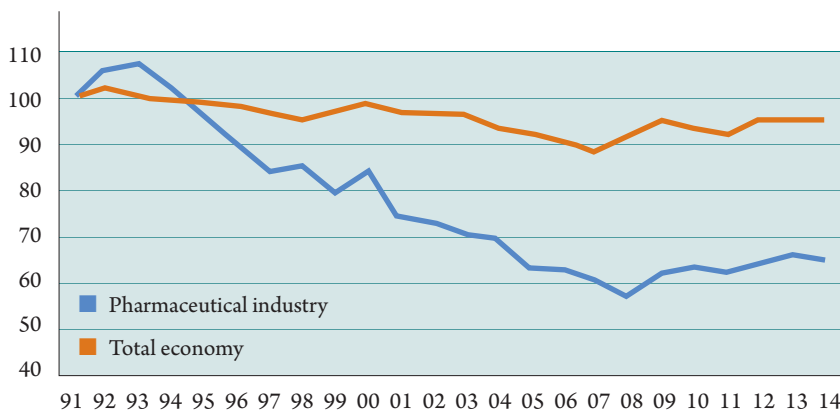
While more than 90% of respondents in the total FAS were satisfied with their work, only two-thirds were satisfied with their salary. This suggests that factors other than the salary contribute to being satisfied with work.

Consistent with previous reports,<sup>1,2</sup> annual income in this survey increased with experience as a medical writer and more advanced job titles.

In particular, the mean salary jumped considerably for writers with >10 years of writing experience. The increase in average income for highly experienced writers is much higher than what was reported in the 2006 survey.<sup>2</sup> This may be due to an ever-increasing demand for highly experienced writers, which increases their market value. However, it may also reflect the fact that the pharmaceutical industry has been reducing spending over the last 20 years.<sup>7</sup> Data from the German statistical office show that the proportion of revenue that pharmaceutical companies spend on their employees as wages (the wage share) began to decrease in the early 1990s and has decreased significantly more than in the total economy, reaching a trough point 9 years ago (Figure 2). (Note that data for this comparison were not available from any of the other main European statistical offices and so only the German data are presented.) Thus, those writers with >10 years of experience started in the industry at a time when pay was generally higher and continue to be paid more now, while those who joined the industry within the last 10 years came in at lower levels and have not received large raises that were previously common.

The upper limit of annual income earned by employed medical writers depended on the type of company they work for. While the starting level income appears to be similar across company types (based on the lower range of incomes reported), the maximum was earned at the three most common employers of medical writers—pharmaceutical, CROs, and medical writing companies. However, both the mean and maximum income was, by far, the highest at pharmaceutical companies. Interestingly, the proportion of writers employed by specialised medical writing companies continued to increase in this survey (21% vs. 19% in 2012 and 3% in 2006). This may reflect a growing employment option for medical writers as more companies become specialised in medical writing.

Importantly, differences in salaries between men and women appear to be disappearing. Whereas salaries were 28% higher for men in 2006 and 15% higher in 2012, they were only 4% higher in this survey. This suggests that the medical writing industry is overcoming sex biases in pay for salaried employees. However, for freelance medical writers, men were charging higher hourly rates than women. Hopefully these data will improve women's awareness of their



**Figure 2. Wage share in the pharmaceutical industry and the total economy in Germany**

Index 1991=100; compensation of employees as % of gross value added.

Source: created from data provided by the German statistical office, and available at [www.destatis.de](http://www.destatis.de) at the time of writing the paper.<sup>8</sup>

market value and give them the courage to charge rates equivalent to their male colleagues.

Unlike the income of employed medical writers, the income of freelance writers did not appear to increase with increased responsibility (through line management activities) or relative to their geographical location; however, the sample size was small, so this may not be a general trend. For freelancers, the only factor that played a role in charging higher hourly rates was experience: those who had worked > 5 years as a medical writer or had an EPDP certificate charged more than those who did not.

Although this analysis included 266 respondents, which represents roughly one-fourth of the EMWA membership, the numbers of respondents in many individual categories assessed was often low. For example, 10 or fewer individuals responded for some countries, employer types, or job titles. As a result, the data from these groups may not be representative of the population as a whole. In addition, the sample may be biased by the type of medical writer who chooses to participate: individuals who earn large amounts tend to be less willing to share financial information, while new medical writers may not yet be members of EMWA (and thus not in the eligible population) or may not yet feel qualified to participate in a survey.

## Conclusions

Overall, the results of this survey were consistent with those of the previous survey for employed medical writers. As medical writers gain experience and take on more responsibility, their salaries increase. The highest salaries were paid for experienced medical writers working for pharmaceutical companies, followed by CROs, and medical writing companies. Salaries were also higher for writers with EPDP certificates. Geographical location may influence annual

income for employed medical writers but appears to play less of a role for the hourly rates charged by freelance writers. The discrepancy in income between men and women has now all but disappeared among employed medical writers, but it continues to be an issue for freelance medical writers, leaving room for improvement.

## Acknowledgements

The authors thank Phillip Leventhal for copy editing and Dirk Schumacher for his input on the discussion of wage shares in the industry. The data collected in this survey are the property of EMWA. The original data are available to EMWA members for purposes of further research, upon reasonable request to the Head Office.

## Conflicts of interest

The authors did not receive compensation for writing this article and declare no conflicts of interest. Julia Forjanic Klapproth and Ansgar Dressler are full-time employees of Trilogy Writing & Consulting, GmbH. Andrea Rossi is a full-time employee of Eli Lilly & Co.

## References

1. Goodwin Burri K. Results of the 2006 EMWA salary survey. *The Write Stuff*. 2006;15(4):133–4.
2. Rossi A, Eichele K. Results of the 2012 EMWA salary survey. *Med Writ*. 2013; 22(3):194–8.
3. Reeves A, Drees B. EMWA freelance and small business survey 2003. *The Write Stuff*. 2004;13(1):11–13.
4. Reeves A, Hamilton S. EMWA freelance business survey 2007. *The Write Stuff*. 2007;16(3):138–40.
5. Reeves A. Third EMWA freelance business survey 2010. *The Write Stuff*. 2010;19(2):147–9.
6. McDonough A, Billiones R, Hamilton S. The fourth EMWA freelance business survey. *Med Writ*. 2013;22(1):67–72.
7. Guatam A, Pan X. The changing model of big pharma: impact of key trends. *Drug Discovery Today*. 2016;21:379–384.
8. Euro Area Core Inflation Rate, 1997–2018. *Trading Economics* <https://tradingeconomics.com/euro-area/core-inflation-rate>.

## Author information

**Julia Forjanic Klapproth, PhD**, has been a medical writer since 1997. As Senior Partner in a company that employs over 40 medical writers, the topics of medical writing salaries, responsibilities, working hours, and motivators are of particular interest for her.

**Ansgar Dressler, Dipl.Stat**, joined Trilogy Writing & Consulting as a medical writer in 2006, after working in the pharmaceutical industry as a biostatistician for approximately 9 years.

**Andrea Rossi** is a biologist who, after a brief spell at the University of Florence, started working in the Italian affiliate of Eli Lilly as a Clinical Research Associate. In the years that followed, he was responsible for Statistics, Health Outcomes and Medical Information. Andrea has been working in medical writing since 2003 with growing responsibilities. Andrea managed the previous EMWA salary survey.



## Appendix. Survey questions

### Demographic information

1. Are you...?
  - a. Male
  - b. Female
  - c. Prefer not to say
2. Where are you employed?  
(list of countries, with option to indicate if they prefer not to specify)

### Education

3. What is the highest academic degree that you hold?
  - a. Associate's degree or below (i.e. an academic degree for a programme of 2 years or less)
  - b. Bachelor's degree or equivalent
  - c. Master's degree or equivalent
  - d. Advanced (MBBS, MD, PhD, MBA or equivalent)
4. In what field of study did you obtain your highest academic degree?
  - a. Biological science (Biology, Biochemistry, Chemistry etc.)
  - b. Healthcare (Medicine, Pharmacy, Public Health, Epidemiology, Nursing, etc.)
  - c. Applied sciences (Mathematics, Physics, Engineering, etc.)
  - d. Humanities (English, History, Journalism, Communications, Technical Writing, etc.)
  - e. Languages, Translation, etc
  - f. Other (please specify):
5. Have you obtained an EMWA professional development programme (EPDP) certificate?
  - a. Yes
  - b. No
6. If yes, which EPDP certificates have you obtained (tick all that apply)?
  - a. The 'original' EPDP multidisciplinary or specialised certificate
  - b. The current foundation level certificate
  - c. The current advanced level certificate
7. Have you completed any other formal training or certification in medical writing (e.g. AMWA certificate, DIA)?
  - a. Yes (specify)
  - b. No

### Work Experience

8. How many years of experience do you have working as a professional in the pharmaceutical/medical/devices industry or associated institutions (e.g. universities)?
  - a. ≤2 years
  - b. >2–5 years
  - c. >5–10 years
  - d. >10–15 years
  - e. >15 years
9. Of these years, how many years have you spent as a medical writer?
  - a. ≤2 years
  - b. >2–5 years
  - c. >5–10 years
  - d. >10–15 years
  - e. >15 years

### Employer Information

10. How would you classify your employer?
  - a. Pharmaceutical company
  - b. Biotech company
  - c. Communications or advertising agency
  - d. Contract research organisation (CRO)
  - e. Association or professional society
  - f. University or medical school
  - g. I am a Freelance (If freelance move to question 13)
  - h. Other (specify)
11. Approximately how many people work for your employer? (Do not answer if freelancer)
  - a. <50
  - b. 50–250
  - c. 251–500
  - d. 501–1000
  - e. 1001–5,000
  - f. >5,000

### Job Information

12. Which of the following departments is your function assigned to in your company? (Do not answer if freelancer)
  - a. Medical Writing
  - b. Medical Affairs
  - c. Pharmacovigilance
  - d. Statistics
  - e. Marketing/Branding
  - f. Clinical Operations
  - g. Regulatory Affairs
  - h. Publishing
  - i. Other (specify)

13. Which of the following best describes your job title?

- a. Associate medical writer
- b. Junior medical writer
- c. Senior medical writer
- d. Principal medical writer
- e. Manager, medical writer
- f. Communication lead/specialist
- g. Publishing scientist
- h. Medical writing scientist
- i. Drug safety specialist
- j. Head of a department
- k. Owner of medical writing company
- l. Freelance
- m. Other (specify)

14. Do you have supervisory responsibilities (e.g. oversight of a project but not line management)?

- a. Yes
- b. No

15. Do you have line management responsibilities?

- a. Yes
- b. No

16. What is your full-time equivalent yearly income before tax deductions? Please specify to the nearest 1,000 Euros using the valid exchange rate for your local currency

17. For Freelancers only: What is your hourly rate before tax deductions? Please specify to the nearest 10 Euros using the valid exchange rate for your local currency

18. Do you work full-time or part-time?
  - a. Full-time (>35 hours per week)
  - b. Part-time (1–35 hours per week)

19. On average approximately how many hours per week do you actually work?

- a. 1–10
- b. 11–20
- c. 21–30
- d. 31–35
- e. 36–40
- f. 41–50
- g. 51–60
- h. >60

20. Thinking of your typical workload, please indicate the proportions of different activities you do from the following:
  - i. Writing

- j. Editing
- k. Translation
- l. Proof-reading
- m. Quality control
- n. Electronic publishing
- o. Supervision (not line management)
- p. Other (please specify)

21. Considering your typical workload, please indicate the proportion of different types of documents that you work on from the following (regardless of whether you write, edit, QC, translate or publish them):
  - q. Documents for clinical and nonclinical development (CSPs, CSRs, SAPs)
  - r. Documents for submission dossiers (CTD Module 2, ISS, ISE)
  - s. Investigators' brochures
  - t. Pharmacovigilance documentation (PSURs/PBRERs, DSURs, RMPs, PADER/PAERs)
  - u. Articles for scientific journals and the scientific press
  - v. Marketing materials, including congress materials and proceedings
  - w. Slide presentations
  - x. Product information
  - y. PIPs/PSPs
  - z. Briefing books
  - aa. SmPCs/PILs
  - bb. Medical and scientific text books
  - cc. Educational materials for patients, including audiovisual media
  - dd. Educational materials for health professionals, including audiovisual media
  - ee. User manuals for devices
  - ff. Consultancy documentation
  - gg. Grant writing
  - hh. Training documentation
  - ii. Other (please specify)

### Job and Salary Satisfaction

22. Are you satisfied with your current work?
  - a. Yes
  - b. No
23. Are you satisfied with your current salary?
  - a. Yes
  - b. No

# Lay writing: Strategies for improving assent forms for children and adolescent participation in health research

Danielle Yuill<sup>1</sup>, Rachel Barron<sup>1</sup>, and Jennifer Preston<sup>2</sup>

1 GW Research Ltd, Cambridge, UK

2 NIHR Alder Hey Clinical Research Facility, Liverpool, UK

## Correspondence to:

Danielle Yuill  
Technical Writer  
GW Research Ltd  
Sovereign House  
Vision Park  
Histon  
Cambridge, UK CB24 9BZ  
+44 (0) 1223 266800  
dyuill@gwpharm.com

## Abstract

Writing for lay audiences is recognised as a difficult task for medical writers, whose specialised knowledge can often hinder effective lay communication. This task is even more challenging when preparing clinical trial information for a paediatric population. Involving advisory groups in the development of clinical trial materials improves their quality and ensures that they are fit for purpose. This article describes how medical writers can build successful partnerships with advisory groups in developing assent forms for children being approached to participate in clinical trials.

Research involving children has more complex considerations than research with adults. Although children are dependent on their parent(s)/legal guardian to provide written informed consent for their participation in clinical trials, they should be involved in the decision-making

process if they have the capacity to assent.<sup>1-4</sup> Assent is, therefore, given by children with capacity, in addition to consent by the legal representative(s), and indicates their understanding of the trial procedures and willingness to participate.<sup>2</sup> In the European Union, while there is consensus regarding the need for assent forms to be adapted in accordance with the age and level of understanding of the children targeted for inclusion, there is discordance regarding the appropriate age of assent and the requirement of a child's signature to confirm their agreement to participate.<sup>5</sup> A medical writer tasked with developing assent form templates for use across multiple countries and multiple trials is, therefore, presented with challenges in negotiating national laws and local practices, as well as trying to ensure the use of appropriate language to aid a child's understanding of a clinical trial.

We advocate partnering with children's advisory groups to overcome some of the challenges of writing for paediatric populations; such partnering is a concept that is newly

emerging in the pharmaceutical industry and often daunting for medical writers to undertake. This article describes the process of assessing the suitability of assent forms and how the support of advisory groups can aid medical writers in preparing clinical trial materials that are fit for purpose.

## Where to start

As medical writers, how do we write assent forms to adequately inform children of differing levels of maturity about participation in clinical trials? How do we know that what we produce provides adequate information to enable a child to make a choice? The internet is an abundant source of information, and there are several examples of ethically approved informed assent forms, which medical writers could use to develop their own company-specific templates. Most of these examples, however, are outdated and do not describe the involvement of children and young people in their development.

We aimed to develop two new assent form templates for use in our paediatric clinical trials that provide sufficient information for children and young people to make informed decisions about participation.

Our original assent form templates (categorised as being suitable for younger children and older children) had been developed in 2013 when we conducted our first clinical trial in paediatric patients. On review in 2016, we determined that there was scope to improve the design and overall comprehensibility of the templates.

Having prior experience with lay writing and the involvement of patient and public groups

An important element of involving lay groups in clinical research is acknowledging the value of the reviewers' input.



in research placed our working group in a good position for carrying out this task.

**Readability**

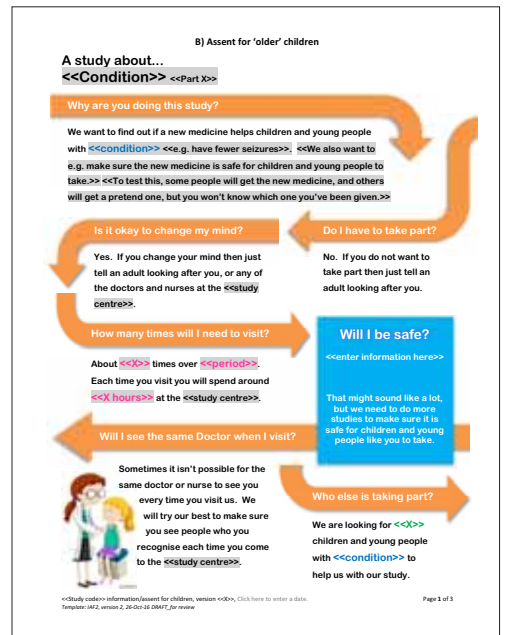
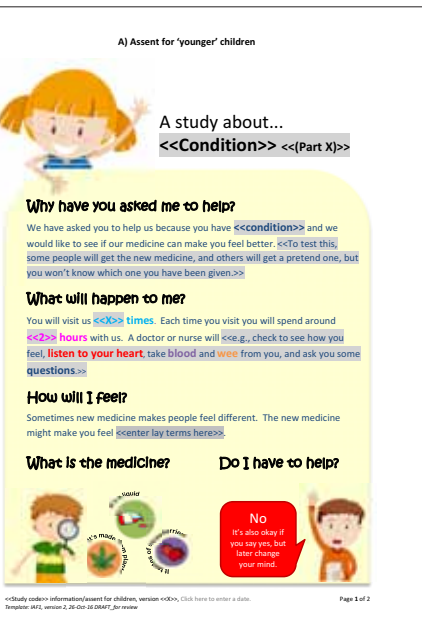
The first step in the redevelopment of the templates was to assess the current readability of the assent forms. Readability tests are designed to measure how difficult a passage of text is to understand, using a formula based on the number of syllables per word and the number of words per sentence. Flesch-Kincaid readability tests are one of the most widely used measures of readability.<sup>6</sup> Using the Flesch-Kincaid grade level (Table 1), our assent form for younger children had a reading grade level score of 6 and our assent form for older children had a reading grade level score of 6.7. Although these readability outputs suggested that our assent forms were *easy* or *fairly easy* to read (i.e. accessible to an *average* 11- to 12-year-old), the difference in grading between younger children and older children was thought to be inadequate, suggesting younger children, in particular, would find our assent forms challenging. Furthermore, as many of our clinical trials involve children and young people with diminished capacity, we felt a score of 6.7 was too high, even for older children.

**The importance of design**

Readability tests can only provide a mathematical assumption of understanding and do not take into account other important factors that contribute to a person's ability to comprehend written text. Such factors include the motivation of the reader, the style of the writer, and the design and layout of the written material.<sup>7</sup> When designing materials for children, we recommend using smaller pieces of information, illustrations or pictures that have meaning, and lots of colour.<sup>8</sup> Although this seems like common sense, few

**Table 1. Flesch-Kincaid grade level scoring**

Flesch-Kincaid grade level score	Age	Reading difficulty
5th	10–11	Very easy
6th	11–12	Easy
7th	12–13	Fairly easy
8–9th	13–15	Standard
10–12th	15–18	Fairly difficult
College	18–22	Difficult
College graduate	>22	Very difficult



**Figure 1. Assent form templates pre-YPAG review**

examples of assent forms available for download on the internet use these basic elements of design.

A key skill in lay writing is the ability of the writer to understand the audience and how the audience interprets information. This is particularly challenging for medical writers when preparing material for children and young people, as they are required to disregard their scientific knowledge as well as best practice in writing for adults, optimising their work for a different generation. This task has added complexities for medical writers with limited personal interaction with children and young people. To overcome these challenges, the involvement of children's advisory groups is recommended.

**From theory to practice**

We revised the language and overall design of our assent forms using the guidance produced by the National Institute for Health Research (NIHR) Medicines for Children Research Network on designing patient information leaflets<sup>8</sup> and the top tips for researchers published by INVOLVE,<sup>9</sup>

a national advisory group supporting public involvement in research.

The revised templates had a Flesch-Kincaid reading level grade score of 4.4 for younger children and 6.1 for older children, an improvement on the previous scores. Regarding design, for younger children we opted for simplicity, using illustrations to make the content appealing. For older children, we used a series of arrows and illustrations to guide users around and down the page to different elements of information regarding the clinical trial (Figure 1).

**Involving lay groups**

Recognising that, as adults, we are not experts in understanding how children and young people think and process complex information, we then contacted the NIHR GenerationR Young Person's Advisory Group (YPAG) to ask for their support in reviewing the revised assent forms. Set up in 2006, GenerationR YPAGs support the design and development of clinical research and have several groups across the UK including Liverpool, Birmingham, London, Bristol, and Nottingham. Each group consists of approximately 10 to 15 members aged 8 to 19 years. The groups meet every 6 weeks during weekends, evenings, or school holidays; research professionals are encouraged to attend the meetings to discuss their findings.

We attended the YPAG at the NIHR Alder Hey Clinical Research Facility, Liverpool, UK, on December 3, 2016. Thirteen children and young people aged 13 to 19 reviewed the assent forms,

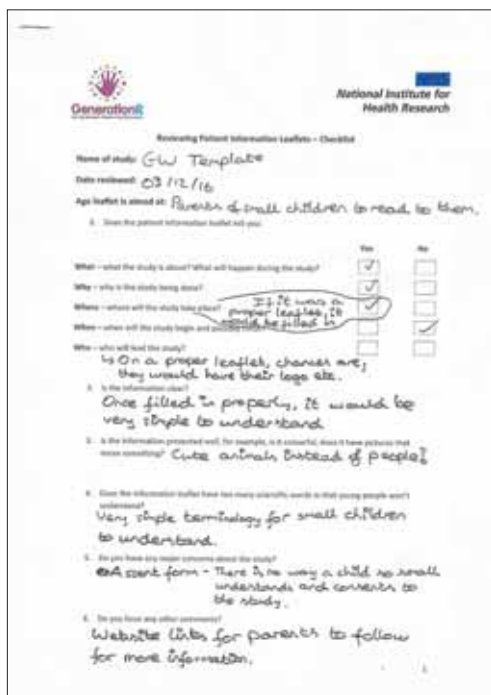


Figure 2. Completed YPAG review form based on assessment of assent for younger children

during which the overall comprehension of the templates was assessed, including design, format, clarity, and readability. Although all reviewers felt

that the information presented in both assent forms was sufficiently *lay* for children and young people to understand, drastic improvements to the designs were suggested by the reviewers to aid overall comprehension and make them more user-friendly. We had detailed discussions with the children and young people on how to achieve this.

### Acting on advice

For younger children, the YPAG suggested “cute animals instead of people” to make the information more reader-friendly (Figure 2). As adults with several years of experience in clinical research, we initially felt that this would be suggestive of animal testing. However, on discussing these concerns with the group, they explained how younger children would not necessarily be aware of animal testing. For older children, the YPAG thought that the “layout [was] confusing with arrows” and suggested a design based on colourful sticky notes and stickers pinned to a notice board.

During our meeting, the group raised an issue regarding the need for a child’s signature on the assent form, as per the International Conference on Harmonisation E11 guidelines (clinical investigation of medicinal products in the

paediatric population).<sup>2</sup> On both assent forms, our initial design used a traditional consent form template with the ethical elements for signature tailored for assent (e.g., “I understand I can stop the study at any time”). For older children, the YPAG altered some of the wording on the signature page to ensure it was understandable. For younger children, however, the YPAG was concerned that they would be unable to understand the elements of assent and provide a signature. To overcome this issue, the group suggested the use of a happy face with a corresponding tick box to acknowledge assent, and a sad face to acknowledge dissent.

### Acknowledging advice

An important element of involving lay groups in clinical research is acknowledging the value of a reviewer’s input.<sup>9,10</sup> Once we had completed the redesign of both assent form templates, we sent a copy of these to the YPAG to show the young people who took part in the review process how we had incorporated their ideas and suggestions (Figure 3).

### Conclusion

The input of children and young people highlighted the value of involving YPAGs or similar groups in clinical trial design and

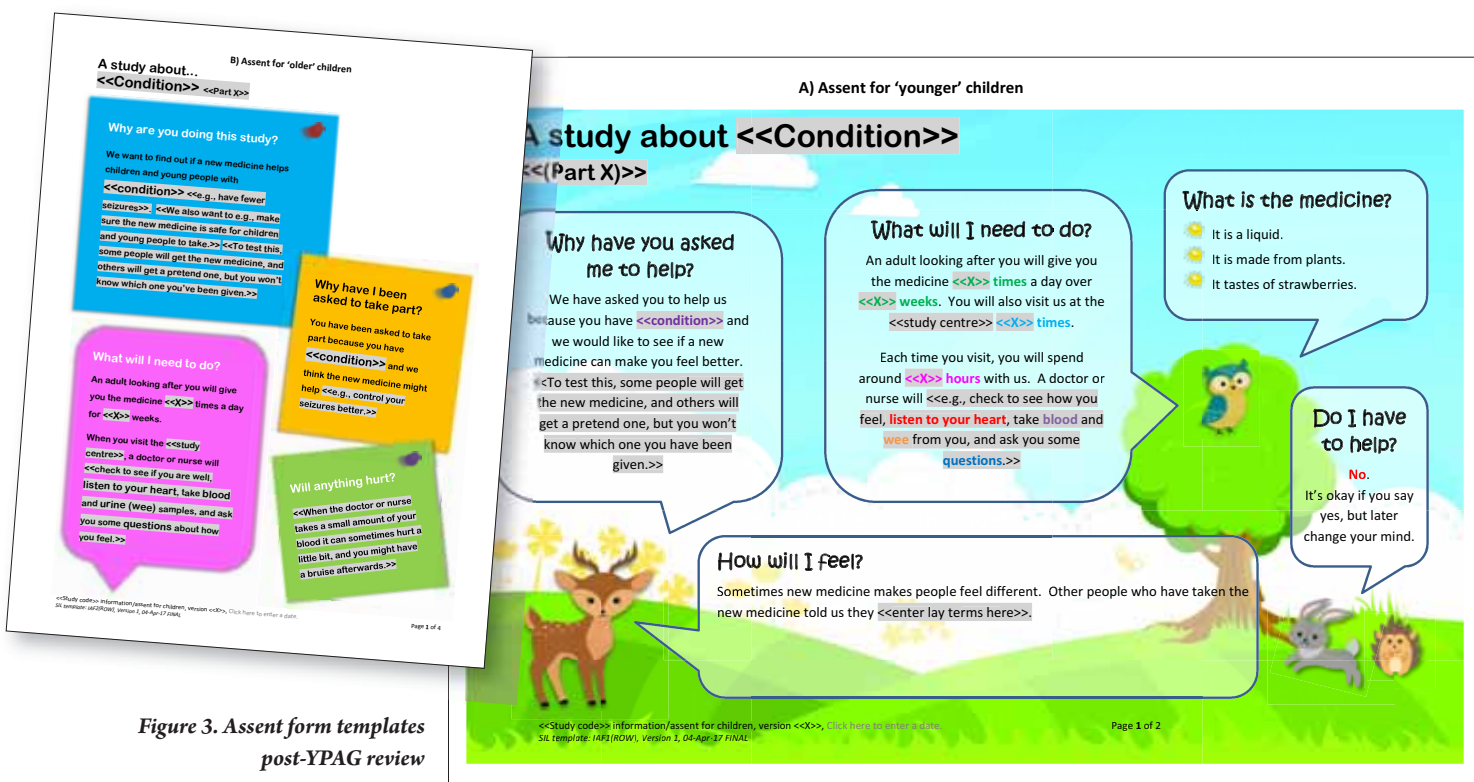


Figure 3. Assent form templates post-YPAG review

development. Although the initial feedback gave testament to our ability to write for lay audiences, and indeed the Flesch-Kincaid scores of our revised templates were aligned with this finding, the overall design of the draft templates affected their suitability. As such, had we not involved the YPAG, although it could be assumed that younger and older children would be able to understand our clinical trials, it is plausible that they would not have engaged with the material, resulting in dissent or potentially subsequent withdrawal post-enrolment.

It should be recognised that there is not necessarily a one-size-fits-all model of assent, as a child's level of understanding will differ on an individual basis. While it is possible to create templates to aid the development of trial-specific assent forms, the decision regarding the suitability of clinical trial materials is ultimately in the hands of the ethics committees from whom approval is being sought. As such, adaptations should be made to templates based on feedback from ethics committees and evidence-based learning and research.

Although writing for children and young people can be difficult, and involving advisory groups can be daunting, medical writers should not be discouraged from pursuing this important area of work. The involvement of advisory groups benefits the paediatric clinical trial process through an improved understanding of clinical trial materials by potential participants and can, in turn, improve medical writers' lay writing skills.

## Acknowledgements

The authors would like to thank all the young people at Liverpool YPAG for their continued support in improving the information that we provide for children and young people taking part in clinical trials.

## Conflicts of interest

The authors declare no conflicts of interest.

## References

1. World Medical Association Declaration of Helsinki. *JAMA*. 2013;310(20):2191–4.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Clinical Investigation of Medicinal Products in the



- Pediatric Population (E11). 2000.
3. US Department of Health and Human Services. Code of Federal Regulations, Title 21 (Food and Drugs) Food and Drug Administration, Part 46 – Protection of Human Subjects, Subpart D, Section 46.408. Accessed 26 July 2016.
4. Giesbertz N, Bredenoord A, van Delden J. Clarifying assent in pediatric research. *Eur J Hum Genet*. 2013;22(2):266–9.
5. Lepola P, Needham A, Mendum J, Sallabank P, Neubauer D, de Wildt S. Informed consent for paediatric clinical trials in Europe: Table 1. *Arch Dis Child*. 2016;101(11):1017–25.
6. Calderón JL, Morales LS, Liu H, Hays RD. Variation in the readability of items within surveys. *Am J Med Qual*. 2006;21(1):49–56.
7. National Institute of Adult Continuing Education. Readability: how to produce clear written materials for a range of readers. Leicester: NIACE; 2009.
8. National Institute for Health Research. Medicines for Children Research Network. Guidance document for researchers designing patient information leaflets. Available at: [http://www.hra-decisiontools.org.uk/consent/docs/MRCN\\_YPAG\\_Guidance\\_for\\_Researchers\\_designing\\_Patient\\_Information\\_Leaflets.pdf](http://www.hra-decisiontools.org.uk/consent/docs/MRCN_YPAG_Guidance_for_Researchers_designing_Patient_Information_Leaflets.pdf).
9. INVOLVE. Involving children and young people in research: top tips for researchers. Eastleigh: INVOLVE; 2016.

10. INVOLVE. Briefing notes for researchers: involving the public in NHS, public health and social care research. Eastleigh: INVOLVE; 2012.

## Author information

**Danielle Yuill** is a technical writer at GW Pharmaceuticals. She has a Master of Research degree in clinical research and experience involving patients and members of the public in the development of clinical trials. She has extensive experience writing and designing clinical trial materials for lay audiences.

**Rachel Barron** is a senior medical writer at GW Pharmaceuticals with an interest in writing for lay audiences. She is a qualified vet who transitioned to medical writing 12 years ago. As such, she has considerable previous experience of communicating medical information to lay audiences (pet owners!).

**Jennifer Preston** is the Patient and Public Involvement (PPI) Manager for the NIHR Alder Hey Clinical Research Facility and PPI Priority Lead for the NIHR Clinical Research Network Coordinating Centre. She set up the first YPAG in Liverpool in 2006, followed by groups throughout the UK, Europe, and the US.





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

An Open Access Resource to Support Authoring of Clinical Study Reports for Interventional Studies



DOWNLOAD THE LAUNCH PUBLICATION: <http://dx.doi.org/10.1186/s41073-016-0009-4>

DOWNLOAD THE USER MANUAL: <http://www.core-reference.org>

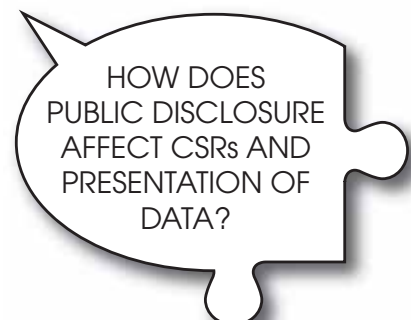
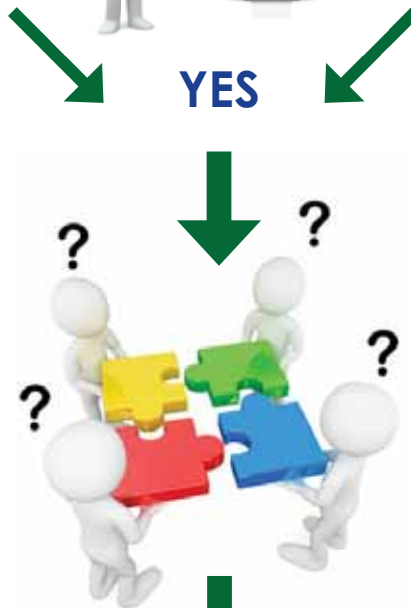
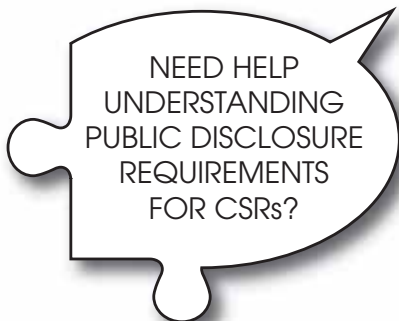


**WRITE OR REVIEW CLINICAL STUDY REPORTS (CSRs)?**

**WRITE OR REVIEW STATISTICAL ANALYSIS PLANS (SAPs)?**



**YES**



## SHARING KNOWLEDGE TO HELP YOU WRITE FIT-FOR-PURPOSE CSRs

### Working in these areas?

- Medical Writing
- Regulatory Affairs
- Statistics
- Clinical Research
- Publication Planning
- Medical Communications
- Clinical-Regulatory Document Public Disclosure
- Regulatory Document Publishing

You should know about: <http://www.core-reference.org>

**Please inform your senior colleagues**

Consider CORE Reference a 'User Manual' that may be used in conjunction with company Standard Operating Procedures to support the authoring of Clinical Study Reports fit for today's modern drug development environment.

# The perils of the unknown: Missing data in clinical studies

Helen Bridge<sup>1</sup> and Thomas M. Schindler<sup>2</sup>

1 AstraZeneca, Cambridge, UK

2 Boehringer Ingelheim Pharma, Biberach, Germany

## Correspondence to:

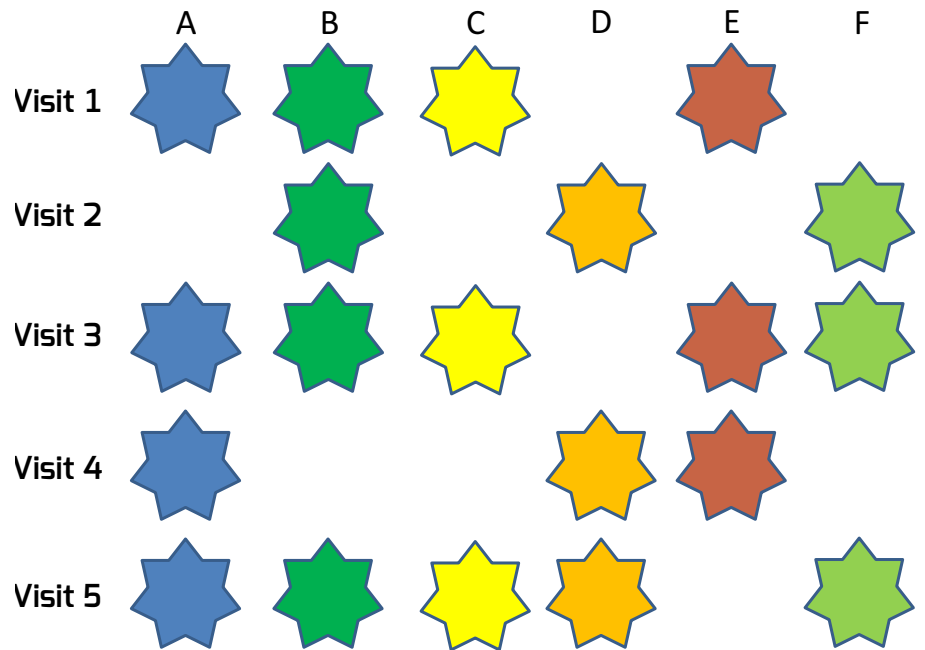
Helen Bridge or Thomas M. Schindler  
Medical Writing Europe  
Boehringer Ingelheim Pharma  
Birkendorfer Str. 65  
88307 Biberach an der Riß, Germany  
Thomas.Schindler@boehringer-ingelheim.com

## Abstract

The phenomenon of missing data is ubiquitous in clinical studies. Both the extent of missing data and the structure of missing data can introduce bias into study results and lead to wrong conclusions. Medical writers should be aware of the extent of missing data and should describe the methods used to deal with the issue. This article outlines some of the most commonly used statistical methods for handling missing data. The traditionally used last-observation-carried-forward (LOCF) method to fill data gaps is problematic in many ways. It is better to employ a method that reduces bias, such as multiple imputation (MI) or mixed-effects models for repeated measures (MMRM). Clinical study design can also help minimise the quantity of missing data.

You may think that this topic does not concern medical writers. You may think this is something for data managers or statisticians. Well, you may need to think again. Every study you write about in a publication or a study report will have dealt with the problem of missing data. Moreover, the way this problem was handled by those conducting the study can have far-reaching

A version of this article previously appeared in the *AMWA Journal* 2017;32(3):116–19, 123.



All rights reserved ©TM Schindler

consequences. The complexity of clinical studies means that everything is related to everything else, so the issue of missing data is linked to many other aspects, from study design to patient retention, data analysis, and the conclusions that can be drawn. Because of this, every scientific report about a clinical study must take note of the extent to which data are missing and how this unfortunate but inevitable fact has been handled.

## Why are data missing in clinical studies?

In an ideal world and an ideal clinical trial, all patients would come to all visits, all patients would take their medication each day at the right time, and all patients would undergo all procedures as planned. No study investigators or patients would move or decide to leave the study, and nobody would have an accident, fall ill, or die during the study. Only in such a scenario could the medical

writer be absolved of having to talk about missing data. But as seen from this non-exhaustive list, in the real world things are never perfect, and the issue of missing data will invariably arise.

## What are the issues?

We cannot assume that we will obtain all the data for all patients in a clinical study. This, however, may or may not be a problem, depending on the quantity and nature of the missing data.

In an ideal world and an ideal clinical trial, all patients would come to all visits, all patients would take their medication each day at the right time, and all patients would undergo all procedures as planned.

There can be no doubt about it: the more data are missing, the shakier the results and conclusions become. It is very difficult to say when a critical limit of missing data has been reached because the size of the study, the indication being studied, the magnitude of difference between treatments, and the frequency and nature of the assessments must all be considered. However, if the trial is testing for a difference in outcome events (e.g. heart

attacks) then even a small number of missing data may be important. If outcome data are missing for a sizable proportion of the patients, the whole trial may become invalid.

A second issue with missing data arises when the pattern of missing data differs between the treatment groups. This is likely to introduce bias in the interpretation of results. Data can be missing for various reasons. On the one hand, it could be pure chance that values are missing. For example, a patient misses a study visit because her car broke down and she could not get to the study site. Or a patient decides to leave the study because he needs to move for his wife to take up a new job in a different region. On the other hand, the fact that data are missing could be related to the outcome that is being measured and/or the study treatment. For example, we might have a much higher dropout rate in one treatment group than in the other. This may happen for many reasons, e.g. because of adverse events, lack of efficacy, or unknown reasons. Often it is difficult to know whether data are missing by chance or because of the treatment. Consider a drug that may cause dizziness and a patient who has a traffic accident on her way to the study clinic and ends up in hospital. Is this a chance event or related to the treatment?

Statisticians have developed a theoretical framework to categorise the reasons for missing data. In brief, they distinguish data that are “missing completely at random (MCAR)” from data that are “missing at random (MAR)” and data that are “missing not at random (MNAR)”. As the elaboration of these concepts is beyond the scope of this short paper, please consult the reading list.

In a randomised trial comparing two treatments, missing data because of chance events should not be much of a

problem, provided they are rare. We would expect chance events to occur with similar frequency in both treatment groups, and therefore no bias is being introduced. However, “missingness” related to the treatment or outcome variable leaves us on very difficult ground.

Suppose we have a study comparing a new wonderdrug (WD) and placebo. WD may cause adverse events that lead to dropout of patients, while patients in the placebo group carry on. Conversely, WD may have good efficacy and no tolerability issues, so the patients taking it remain in the study, while patients in the placebo group drop out because they see no improvement. In these scenarios, we risk underestimating or overestimating the size of the treatment effect.

Differential withdrawal between treatment groups will result in a serious conceptual problem. The goal of randomisation is that the two treatment groups will have similar characteristics at the start of the study. If many patients in one group but not in the other withdraw from the study, the two groups may no longer be comparable at the end. If a sizeable proportion of patients in the WD group drops out because of tolerability issues, we will not only have more missing data in this group, we will also have a different group of people at study end. By exposing patients to WD for some weeks, we unintentionally “select” those patients who are able to tolerate the treatment. Hence, at study

end we arrive at a comparison of the placebo group with all its initial demographic and disease characteristics and a modified WD group that consists only of those patients who have tolerated the treatment. Their demographic and baseline disease characteristics may be quite unrepresentative of the initial population. This will

make it very difficult to draw any conclusions about the efficacy or safety of WD.

When reporting clinical studies, medical writers need to be alert to signs that missing data are not due to chance and therefore have the potential to cause bias. Signs to watch out for include differences between treatment groups in the proportions of patients with missing values or the reasons for withdrawals. Clusterings of withdrawals or missed visits around certain points in time should also raise suspicion. A starting point could be the tables detailing the disposition of patients. If you detect any issues, it is advisable to ask the statistician to provide further information on the missing data.

Now let’s look at an example of what missing data can look like for individual patients. Let’s assume that we are looking at a trial in patients with type 2 diabetes. We want to find out what effect our new drug has on the long-term marker for blood sugar levels, haemoglobin A1c (HbA1c). We are looking at the change from baseline to study end as our primary endpoint for efficacy. Table 1 depicts the data of five patients.

In this example, we have all values only for patient 1, who has completed all visits. Thus only for her can we easily calculate the change from baseline. Data analysis will be more complicated for the other four patients because they have data missing for some visits. Would it therefore be a good idea to ignore the data from patients 2 to 5, i.e. concentrate the analysis only on “completers”? No, it would not. Looking at the table does not tell us the reasons why the data are missing, and this is a common situation in clinical trials. We may know the broad reasons why some patients withdrew (e.g. “adverse event” or “lack of efficacy”) and the reason why a patient died, but patients who are lost to follow-up or who missed some visits may not have detailed reasons recorded. The patients who missed visits in our example may have done so because of the severity of their disease, or because they had

**When reporting clinical studies, medical writers need to be alert to signs that missing data are not due to chance and therefore have the potential to cause bias.**

**Table 1. Data from 5 patients in a study with the primary endpoint of change from baseline in HbA1c**

	Study start / Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5/ Study end	Comment
Patient 1	X0	X1	X2	X3	X4	X5	Completer
Patient 2	X0	X1	X2	–	–	–	Withdrew at Visit 2
Patient 3	–	X1	X2	X3	X4	X5	No baseline value
Patient 4	X0	X1	X2	X3	–	–	Died after Visit 3
Patient 5	X0	–	–	–	X4	–	Did not attend all visits

adverse events, or because of chance events having nothing to do with their health. The patients who attended all visits could be the younger patients with fewer comorbidities who are fit and mobile enough to make it to every planned visit. If we focus on the “completers” (or “observed cases”), we may be selecting patients who are not representative of the population as a whole. Disregarding all the patients with incomplete data would not only risk bias, but would also make us lose a lot of valuable information.

### What can we do about missing data?

A number of different statistical methods exist for handling missing data, and the risk of bias in a particular situation will vary depending on the method chosen.

#### Simple imputation methods

For both ethical and economic reasons it would be wise to use all the data we have gathered during a clinical study. Thus we need to find the best and most appropriate ways to use the data. One method that has been used for many years is the “last-observation-carried-forward” approach, or LOCF. The LOCF method is very simple as it fills in (or “imputes”) the missing data items with the last observation that was obtained at a previous time point (Table 2).

After having performed LOCF, we can now easily calculate the change from baseline to study end (for patient 3 we use the data from Visit 1 as a starting point). This method looks convenient as it fulfils our aim to include all patients in the analysis and provides a mechanism for filling in the missing values. (A similar imputation method is BOCF, i.e. “baseline observation carried forward”. Here a patient’s baseline value is carried over.)

Although appealing in its simplicity, the LOCF method is likely to introduce bias and may

even lead to wrong conclusions. Suppose, for example, we perform a study in a population of patients with depression. Typically, in a group of patients with depression some will improve spontaneously in their condition. If many patients in the active treatment group in the study drop out because of adverse events and the LOCF method were applied, this would likely result in underestimation of the treatment effect of the drug. The reason for this is that not all the spontaneous improvements in the active treatment arm would have had a chance to surface and be recorded. Conversely, suppose we perform a study in a population of patients who have a condition that worsens over time. The condition in the group of patients that received placebo would continue to worsen, resulting in a worse score at study end. If some patients in the active treatment group leave the study prematurely due to adverse events, the LOCF method would mean using an earlier, better score for these patients than the scores they would have had at study end, had they stayed on study as their condition continued to worsen over time. This would likely favour the active treatment and result in overestimation of the treatment effect. Because of its potential for introducing bias and leading to incorrect conclusions, regulators and leading statisticians urge clinical researchers to stop using the LOCF method.

#### Methods involving statistical modelling

Instead of filling in each missing value with a single “replacement” value (as with LOCF and BOCF), more sophisticated methods of handling missing data exist that use statistical modelling to minimise bias. The multiple imputation (MI) method involves using all the data collected in all patients, whether they have complete data or some missing values, to model the distribution

No amount of statistical expertise can make up for the absence of real data.  
– MG Kenward

of the missing data. This model is then used to generate a series of values (this is the “multiple”) to fill in each missing observation. An overall estimate of treatment effect is derived by combining all the results.

A different approach to handling missing data is to use a model for the analysis that can take account of all the available information from patients with complete data as well as those with some missing values. This makes it unnecessary to fill in the missing values with substitute values. Such an approach, called mixed-effects models for repeated measures (MMRM), is frequently used in clinical trials where the same continuous outcome variable is measured repeatedly at different time points. In effect, these analyses combine the information available for patients who have missing data with information from the patients who have complete data to predict what the responses of the patients with missing data would have been.

Suppose a patient showed a small improvement from baseline early in the trial then withdrew after 3 weeks, while most other patients in the same treatment group had larger improvements in the first 3 weeks and then continued to improve until the end of the study. In an MMRM analysis, the pattern seen in the data collected from the patient before withdrawal will feed into the overall estimate of treatment effect, as will all of the data collected from the other patients. So in this example, the model will assume that the withdrawn patient, like the other patients, would have continued to improve after Week 3, but – based on the data from the first 3 weeks – that this patient’s improvement would have been smaller than average.

By comparison with single imputation methods like LOCF and BOCF, MI and MMRM have the clear advantage of using all the available

Table 2. Data from 5 patients in a study with the primary endpoint of change from baseline in HbA1c with missing data being filled in by LOCF

	Study start / Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 / Study end	Comment	
Patient 1	X0	X1	X2	X3	X4	X5	Completer	
Patient 2	X0	X1	X2	—————→		X2	Withdrew at Visit 2	
Patient 3	–	X1	X2	X3	X4	X5	No baseline value	
Patient 4	X0	X1	X2	X3	—————→		X3	Died after Visit 3
Patient 5	X0	–	–	–	X4	X4	Did not attend all visits	

information for each patient (i.e. all of the values in Table 2 instead of just one value) to arrive at an estimate of treatment effect. Both methods have also been shown to produce much less biased estimates than LOCF.

### Sensitivity analyses

There is no single best solution to the missing data problem that will produce unbiased results in all circumstances. As well as choosing a method that is appropriate to the particular situation, it is important to investigate the robustness of the results by carrying out sensitivity analyses. These should include analyses using missing data handling methods that rely on different assumptions from the method that was used in the primary analysis. For example, if MMRM is used for the primary analysis, the sensitivity analysis might include MI and sophisticated modelling techniques that do not make the same assumptions as MMRM about the nature of the missing data. If the results from the primary analysis and the various sensitivity analyses are similar, then we can be confident that the results are not being unduly influenced by the method used for handling missing data. If, on the other hand, the results differ substantially, then the issue of missing data needs further investigation and discussion.

## What can be done to avoid missing data?

*No amount of statistical expertise can make up for the absence of real data.* – MG Kenward

Preventing missing data in the first place therefore needs to be a top priority. A number of measures can be taken at the trial protocol stage to help limit the quantity of missing data. Most importantly, trials need to be designed so that they interfere only minimally with the “normal life” of the study participants. That means study visits should be scheduled at convenient times and should not take too long. If it is possible to minimise the number of visits and assessments in the trial, this is likely to help retain patients. Likewise, generous visit windows make it easier for patients to fit study visits around other commitments. The longer the follow-up period, the more patients are likely to withdraw, so using a short follow-up period, at least for the primary endpoint, can help minimise the impact of missing data. Endpoints that are difficult or time-consuming to measure, or that require invasive procedures, tend to result in a high quantity of

missing data. If endpoints can be chosen that are easy to measure, this is likely to reduce the amount of missing data.

As we have seen, missing data that arise due to adverse events or lack of efficacy are especially problematic because they tend to be associated with a particular treatment and therefore risk biasing the results of a study. Withdrawals due to tolerability issues can be minimised by allowing flexible dosing. Withdrawals due to lack of efficacy are a common problem when patients receive placebo, so using an add-on design, where patients receive active treatment or placebo in addition to standard treatments, can help to avoid withdrawals for this reason. Should a patient nevertheless need to discontinue study treatment, the sponsors should ask for permission to continue to collect data from them and plan the study so that discontinuation of treatment does not necessarily mean the patient has to withdraw from the study.

During trial conduct too, precautions can be taken to limit missing data. Engaging the participants by giving clear explanations of the study purpose and the procedures will most likely reduce the number of patients who withdraw from the study.

Realistically, it will never be possible to prevent missing data altogether. In order to ensure that data are collected from enough patients to enable valid conclusions to be drawn, it is important to consider the likely number of missing values when planning the trial and to allow for them when calculating how many patients to recruit.

### Disclaimers

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

### Conflicts of interest

The authors declare no conflicts of interest.

## References

- Committee for Medicinal Products for Human Use (CHMP). 2010. Guideline on missing data in confirmatory clinical trials. EMA/CPMP/EWP/1776/99 Rev. 1.
- Kenward MG. The handling of missing data in clinical trials. *Clin Invest*. 2013;3(3): 241–50.
- Little RJ, D’Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med*. 2012;367(14):1355–60.
- Mallinckrodt CH, Sanger TM, Dubé S, DeBrotta DJ, Molenberghs G, Carroll RJ, et al. Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. *Biol Psychiatry*. 2003; 53:754–60.
- National Research Council. 2010. The prevention and treatment of missing data in clinical trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press.
- O’Neill RT, Temple R. The prevention and treatment of missing data in clinical trials: an FDA perspective on the importance of dealing with it. *Clin Pharmacol Ther*. 2012;9,3:550–4.

### Author information

**Helen Bridge, DPhil**, was previously a university lecturer in German language and literature. She then studied life sciences with statistics at the Open University, and became a regulatory medical writer in 2012. She worked in a CRO for 6 years before moving to AstraZeneca in March 2018.

**Thomas M. Schindler, PhD (Molecular Physiology)**. After his post-doc, he went into publishing as a popular science editor and has now gained some 20 years of experience in both medical affairs and regulatory medical writing. He is the head of the European regulatory medical writing group at Boehringer Ingelheim Pharma.

# Medical writing in China: Trends and opportunities

**Yanni Wang**

International Biomedical Communications,  
LLC, Frederick, MD, USA

## Correspondence to:

Yanni Wang, PhD

International Biomedical Communications,  
LLC

Frederick, MD, USA

+1 240 608 2380

dr.yanni.wang@gmail.com

## Abstract

The Chinese pharmaceutical regulatory landscape and medical publication policies have gone through drastic changes in recent years, and they continue to evolve. These changes provide great opportunities and many challenges to medical writers in China, and they affect the global medical communications strategy of multinational pharmaceutical companies and global medical communications agencies. Seasoned medical writers who are fluent in both English and Chinese are becoming essential to multinational pharmaceutical companies interested in the Chinese market as well as to Chinese companies striving to enter the global market. Meanwhile, the demand for ethical medical writing and editorial services remains high. In this article, I share my observations on the current trends, opportunities, and challenges facing medical communications professionals in China.

## Background

The Chinese pharmaceutical industry has experienced tremendous growth in the past decade, and China has become the second largest pharmaceutical market in the world. According to a report published by the US Department of Commerce, the Chinese pharmaceutical market is projected to grow from \$108 billion in 2015 to \$167 billion by 2020.<sup>1</sup> Meanwhile, China's total healthcare expenditures have increased rapidly and are projected to almost double by 2020 (Figure 1).

Behind the rapid growth of the Chinese pharmaceutical industry are two forces. One is that multinational pharmaceutical companies continue to increase their investment in China and the second is that a growing number of Chinese biopharmaceutical companies strive to improve their reach both at home and globally.

In the past, global and local pharmaceutical companies have faced many challenges in China. One of the main challenges has been the uncertainty of Chinese drug regulation. The Chinese government's unique regulatory requirements, the lack of clear guidance, and the ever-changing rules often cause headaches for both foreign and domestic companies.

However, things began to change in June 2017. During the International Council on Harmonisation meeting in Montreal between May 31 and June 1, the China Food and Drug Administration (CFDA), which is the Chinese pharmaceutical regulatory authority, was approved as a regulatory member.<sup>2</sup> This marks a significant milestone in China's pursuit of regulatory modernisation. It also provides many opportunities and challenges for all pharmaceutical companies operating in China.

Meanwhile, the Chinese Center for Drug Evaluation, a division of the CFDA, is leading an effort to translate many of the US FDA guidelines into Chinese. This will serve two purposes. First, this will help the staff at CFDA and the Chinese Center for Drug Evaluation learn the lessons and gain from the experience of the US FDA. After all, the regulatory bodies face many similar challenges. Second, the translated documents will greatly help Chinese pharmaceutical companies planning to bring their products to global markets.

The recent changes in the Chinese regulatory landscape will inevitably affect many functional areas of the Chinese pharmaceutical industry. Along with manufacturing and clinical trial management, medical writing – especially regulatory medical writing – will face drastic changes.

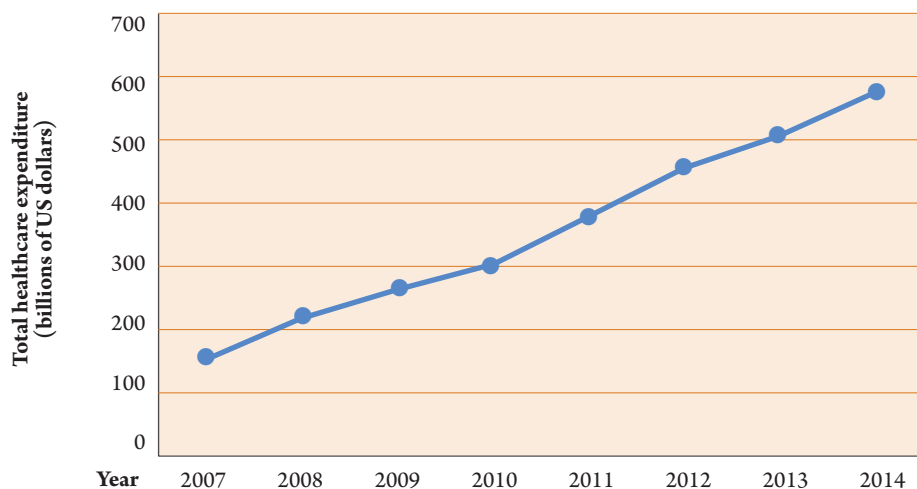
## The rise of the Chinese regulatory medical writing profession

### The past

Regulatory medical writing is a new profession in China. This is not because the need for regulatory medical writing did not exist in China a decade ago. Rather, regulatory medical writing was only recently recognised as a profession.<sup>3</sup> In the past, most Chinese pharmaceutical companies did not have dedicated medical writing employees. Regulation-related medical writing was often managed by larger departments, such as medical affairs or clinical development.

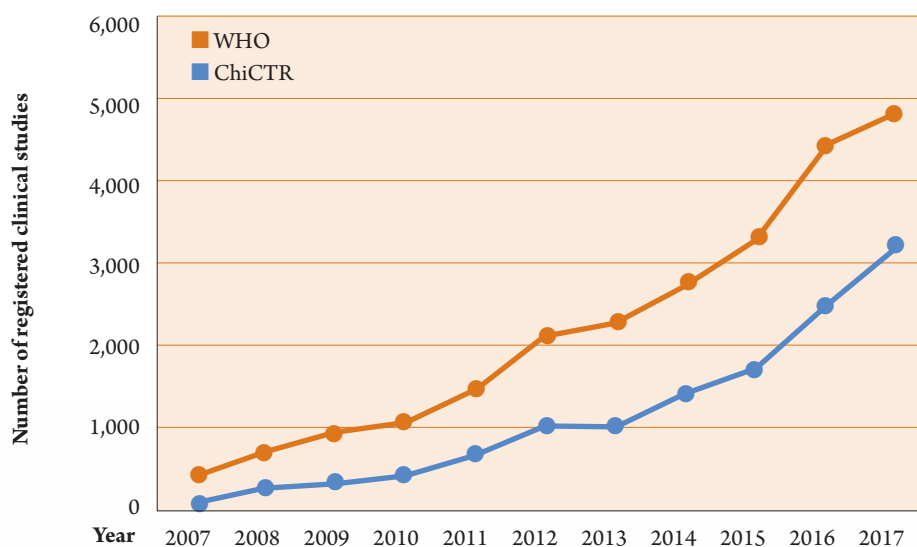
Employing professional regulatory medical writers to prepare regulatory documents is believed to have been introduced by multinational pharmaceutical companies entering the





**Figure 1. China's total healthcare expenditure from 2007 to 2014 in current US dollars**

Data are from the WHO<sup>15</sup>



**Figure 2. Number of clinical studies recruiting Chinese subjects**

Data are from the WHO<sup>16</sup> and the Chinese clinical trial registry (ChiCTR).<sup>17</sup>

Data for 2017 are up to December 12.

Chinese market. Even though the companies had medical writers based in the headquarters developing documents for global submissions,

they still needed a bilingual local work force to work with internal colleagues and the CFDA. Regulatory medical writers who can speak and

write well in both English and Chinese are in great demand.

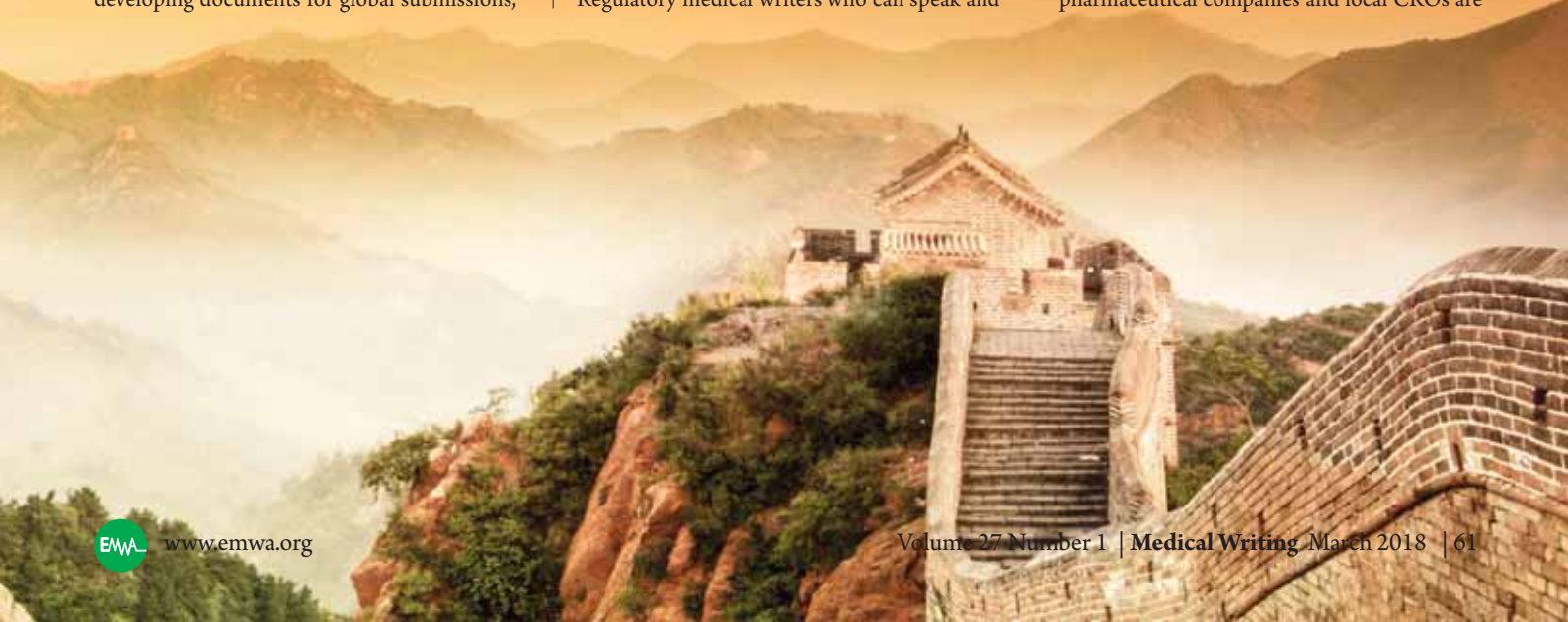
At first, global pharmaceutical companies turned to China-based contract research organisations (CROs) to help with medical writing-related projects. The quality of the deliverables from these CROs, however, was inconsistent when medical writing was not one of their core competencies. Gradually, multinational pharmaceutical companies, especially those that had set up research and development centres in China, started to build their own local medical writing teams. As they began to hire and train Chinese medical writers, the concept of professional medical writing became better known to the Chinese pharmaceutical industry.

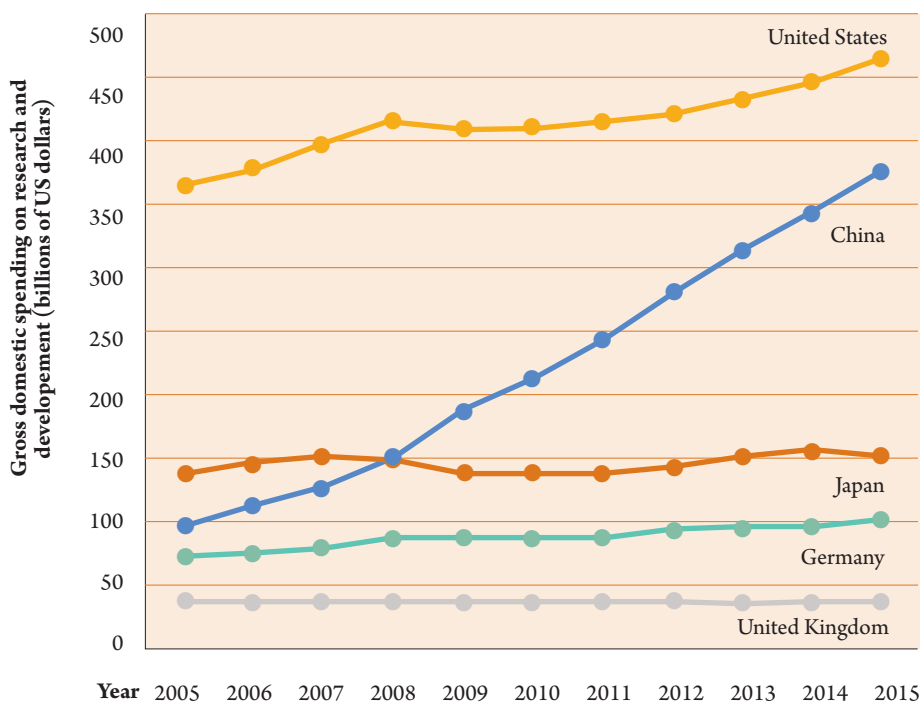
**The present**

Although accurate data are lacking, the number of professional regulatory medical writers in China is generally believed to have been fewer than a few dozen a few years ago, most of whom worked for multinational pharmaceutical companies and global CROs.<sup>4</sup> Current estimates suggest at least a few hundred Chinese regulatory medical writers work for foreign companies and local companies alike, and the number is expected to grow rapidly in the next few years.

To support the growing number of local medical writers, in 2013 a group of medical writers based in China proposed and subsequently established the China Medical Writers Community (CMWC).<sup>5</sup> The formation of CMWC marks the birth of regulatory medical writing as a profession in China. Membership in the CMWC has grown steadily. In addition to biannual educational events, CMWC members actively share knowledge and expertise online through a social media group.

In addition to multinational pharmaceutical companies and global CROs, Chinese biopharmaceutical companies and local CROs are





**Figure 3. China's gross domestic spending on research and development**  
Data are from the Organisation for Economic Co-operation and Development.<sup>18</sup>

also contributing to the growth of the regulatory medical writing profession in China. Many of these Chinese biopharmaceutical companies and CROs are startups founded and managed by Chinese overseas returnees. Before returning to China, the owners and the management teams of these companies often had worked at global pharmaceutical giants for many years. Many of them have decades of research as well as management experience, and they understand the importance of high-quality clinical and regulatory documents in drug development and marketing submissions. When they need clinical trial protocols, clinical study reports, and Common Technical Documents (CTDs), they turn to professional medical writers for help in producing high-quality deliverables.

#### The future

As the Chinese government continues its support for drug development and strives to modernise its drug approval process, more products will be developed and more clinical trials will be conducted in China (Figure 2). This means that more professional medical writers will be needed.

Currently, most medical writers in China work for pharmaceutical companies, CROs, or large medical device companies. As the field continues to grow and as the first generation of medical writers gains more experience, some may choose to freelance or work as contractors. The idea of becoming a freelance medical writer may

sound unimaginable to many Chinese medical writers right now, but in a few years it will not be.

#### Opportunities and challenges

When the CFDA begins to implement the CTD and require eCTD submissions for regulatory submissions in China, the need for medical writers experienced with CTDs will increase. However, few Chinese medical writers possess this skill. Many local Chinese medical writers therefore will face short-term challenges and a steep learning curve, but with adequate training and guidance, they should quickly be able to overcome the challenges. Once they have become proficient, they will be able to contribute more to submissions, whether China-specific or global.

The shortage of qualified medical writers provides many opportunities to experienced medical writers outside of China. Leading a medical writing team in China and providing training services to local medical writers are just two examples of these opportunities.

### The evolving landscape of academic scientific publishing in China

#### Publication boom and misconduct

The number of scientific journal articles published by Chinese scholars has skyrocketed in the past decade.<sup>6</sup> This publication boom is the result of the Chinese government's enhanced

support for science and research, coupled with the continued push for scientific publication by universities and research institutions (Figure 3). In addition to providing funding, many universities and research institutes offer a range of publication-related incentives, including name recognition, career advancement, and monetary awards, also known as cash-for-publication policies.<sup>7</sup>

However, with the push for more publications, especially in high-impact English journals, publication misconduct has become a problem.<sup>8</sup> Recent scandals have tarnished the integrity and reputation of Chinese research. These incidents have triggered prompt investigations and crackdowns from the Chinese government agencies, including the China Association for Science and Technology.<sup>9</sup> The investigations have exposed plagiarism, data falsification, authorship purchasing, manipulation of the peer-review process, and other kinds of misconduct. Determined to improve the integrity and reputation of Chinese research and scientific publishing, the China Association for Science and Technology has developed and is implementing a series of programmes to prevent fraud.<sup>10,11</sup>

#### Challenges of scientific writing and publishing for Chinese scholars

Many researchers dread writing journal articles. If you ask, some of them might jokingly tell you that this is because they are pursuing science, not writing! Because of language barriers, writing in English adds another layer of challenges to many Chinese researchers.

To increase the likelihood of being published in English-language journals, many Chinese researchers seek editorial assistance from individual editors or editorial agencies. This has fuelled the increase in the number of editorial service providers in China. How many editing companies are operating in China is unknown, although a recent statement by the Alliance for Scientific Editing in China suggests that close to a thousand companies offer English writing and editing services to Chinese scholars.<sup>12</sup> Only a handful of these, however, are believed to be providing transparent and ethical services.

#### Challenges and opportunities for editorial service providers

Research and publication misconduct by some researchers in China has tarnished the image and



reputation of all of the editorial service providers. Researchers are frequently unfamiliar with guidelines on publication ethics, and may confuse legitimate and ethical medical writing services with spurious and improper services. As a result, many Chinese researchers hesitate to admit and acknowledge medical writing and editing support.

Despite research misconduct and publication-related scandals, the demand for legitimate medical writing and editing services will continue to remain high in China. The challenge facing providers is to deliver satisfactory services while protecting their reputations and receiving deserved recognition for their work.

The Chinese government is making great efforts to enhance research integrity in China.<sup>13</sup> Many leading Chinese researchers and government officials fully understand the importance of research and publication integrity and deeply care about their reputation. Through carefully planned educational programmes, updated publication guidelines, and enhanced government regulations, the quality of scientific publishing in China will improve, although it will take time.

Companies providing ethical and quality medical writing and editing services will need to make great efforts to distance themselves from the so-called “paper brokers”<sup>8</sup> and to maintain high ethical standards. When necessary, they will need to educate the researchers they serve and encourage them to follow the guidelines of international journals, such as the guidelines of the International Committee of Medical Journal Editors.<sup>14</sup> Building a transparent, ethical, and trustworthy relationship between legitimate editorial service providers and Chinese researchers will benefit all parties.

## Summary

With the Chinese government’s continued support for drug development and its determination to modernise its drug approval process, the Chinese pharmaceutical industry and the regulatory writing profession will continue to grow. Experienced medical writers who are familiar with the CTD format and who can both write well in English and understand Chinese will be of great value to pharmaceutical companies interested in accessing the Chinese market.

At the same time, the biomedical publishing industry will continue to grow in China. Recent scandals have caused concerns about the quality of scientific research conducted in China, but with enhanced regulation and extensive educa-

tion, the situation will gradually improve. Ethical and high-quality medical writing and editing support is and will continue to be in high demand.

## Acknowledgements

The author thanks Dr Hongbo Zhu for reviewing the manuscript and providing insightful comments.

## Conflicts of interest

The author works with clients in the global pharmaceutical and healthcare industries.

## References

- 2016 Top markets report pharmaceuticals country case study [cited 2017 October 10]. Available from: [https://www.trade.gov/topmarkets/pdf/Pharmaceuticals\\_China.pdf](https://www.trade.gov/topmarkets/pdf/Pharmaceuticals_China.pdf).
- ICH assembly, Montreal, Canada, May/June 2017 [cited 2017 October 11]. Available from: <http://www.ich.org/ichnews/press-releases/view/article/ich-assembly-montreal-canada-mayjune-2017.html>.
- Feng L, Amano E. Regulatory writing: medical writing in China and Japan. *Med Writ*. 2013;22(2):143–6.
- Cooper J. Medical writing services in Asia: recent development and trends [cited 2017 October 10]. Available from: <https://www.pharmaceutical-tech.com/articles/medical-writing-services-in-asia-recent-developments-and-trends>.
- Committee CMWCS. Growing demand for professional medical writing in China and the new china medical writers community. *AMWA J* 2015;30(3):126–8.
- Van Noorden R. China by the numbers. *Nature*. 2016;534(7608):452–3.
- Quan W, Chen B, Shu F. Publish or impoverish: an investigation of the monetary reward system of science in China (1999–2016). *Aslib Journal of Information Management*. 2017;69(5):1–18.
- Henry BA. The past and present of research integrity in China [cited 2017 October 11]. Available from: <http://www.the-scientist.com/?articles.view/articleNo/48577/title/The-Past-and-Present-of-Research-Integrity-in-China/>.
- Normile D. China cracks down after investigation finds massive peer-review fraud 2017 [cited 2017 October 11]. Available from: <http://www.sciencemag.org/news/2017/07/china-cracks-down-after-investigation-finds-massive-peer-review-fraud>.
- Frankel MS, Leshner AI, Yang W. *Handbook of Academic Integrity*: Springer; 2016.
- Yang W. Policy: boost basic research in China [cited 2017 October 11]. Available from: <https://www.nature.com/news/policy-boost-basic-research-in-china-1.20117-/b3>.
- Proposal on the establishment of standards for editing English scientific articles in China [cited 2017 October 11]. Available from: <http://www.mrpcenter.com/mrp/1-3/read/1-3-26.html>.
- Yang W. Research integrity in China. *Science*. 2013;342(6162):1019.
- International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals [cited 2017 November 4]. Available from: <http://www.icmje.org/icmje-recommendations.pdf>.
- Global health expenditure database [cited 2017 October 26]. Available from: <http://apps.who.int/nha/database/ViewData/Indicators/en>.
- International clinical trials registry platform [cited 2017 October 26]. Available from: <http://apps.who.int/trialsearch/AdvSearch.aspx>.
- Chinese Clinical Trial Registry 2017 [cited 2017 October 25]. Available from: <http://www.chictr.org.cn/>.
- Gross domestic spending on R&D [cited 2017 October 26]. Available from: <https://data.oecd.org/rd/gross-domestic-spending-on-r-d.htm>.

## Author information

**Yanni Wang**, PhD, CMPP, is a bilingual English and Chinese medical writer and the owner of International Biomedical Communications (IBC), a US-based company dedicated to translating research data into clear messages. Yanni and her team at IBC have extensive experience in developing a wide range of medical content for global clients in the US, China, and Europe.

# PhD student: A medical writer in the making!

## Somsuvro Basu

Institute of Cytobiology and Cytopathology  
Philipps University Marburg  
Marburg 35032, Germany

### Correspondence to:

Somsuvro Basu, PhD  
Institute of Cytobiology and Cytopathology  
Philipps University Marburg  
Robert Koch St. 6  
35032 Marburg, Germany  
+4915731972527  
Email address: basu.somsuvro@gmail.com

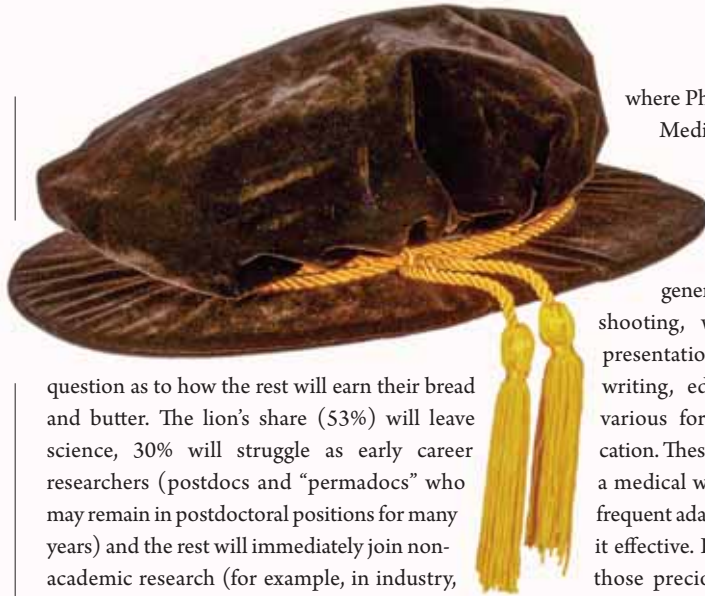
### Abstract

With the ever-increasing stock of PhD holders and the diminishing number of permanent academic positions, alternative careers are in demand. Before the impostor syndrome marches in, these graduates need to realise that there can be a bright future, which is even possible outside of academia. However, they require appropriate guidance to find their true calling. Medical writing could be a perfect fit for many with a background in life sciences. During their research years, PhD students acquire key skills that could be cornerstones of a medical writer's portfolio. Unfortunately, they may not realise this right match until it is too late. In this article, I discuss the precious dexterities of PhD students that could shape them as medical writers. As an added bonus, certain tricks and practices are revealed to complement this intriguing process.

### Introduction

In Germany, 28,147 PhD researchers (referred henceforth as "PhDs") wore their graduation hats in 2014.<sup>1</sup> Do you know how many of them will eventually use the title "Professor" in front of their names? Most probably, no more than 130!<sup>2</sup> Yes, you read it correctly.

The US, the biggest spender in research and development (R&D),<sup>3</sup> produced a staggering 54,070 PhDs in 2014.<sup>1</sup> Only a relatively few of these bright minds will receive the laurel wreath of professorship. Hence, this raises the immediate



question as to how the rest will earn their bread and butter. The lion's share (53%) will leave science, 30% will struggle as early career researchers (postdocs and "permadocs" who may remain in postdoctoral positions for many years) and the rest will immediately join non-academic research (for example, in industry, non-profit organisations, government).<sup>2</sup> Eventually, most of the postdocs will leave science or join the non-academic sector, while a minuscule proportion will end up as permanent researchers or professors.<sup>2</sup>

I am addressing the 47% of PhDs who wish to stay in science. You have to strike while the iron is hot! You need to learn how to avoid the impostor syndrome (self-doubts regarding your worthiness)<sup>4</sup> and learn how to defeat the mental health challenges that nearly one-third of PhDs suffer from.<sup>5</sup> However, these obstacles can't be enough to shatter PhDs' exceptional characteristics. PhDs are a unique horde of individuals. Less than 2% of the world's population possess a PhD degree.<sup>6</sup> Therefore, have confidence in yourself and trust the precious skills you developed during your PhD or postdoc years.

The world outside academia needs your expertise. There are several areas in industry where PhDs can shine without having any prior industry experiences. The most popular sphere befitting a PhD is R&D. However, the time has come when other alternative roles have become attractive. I am specifically highlighting a domain

where PhDs have proved their mettle.

Medical writing! Does it ring a bell? Not yet? Then imagine a typical week of a PhD student or postdoc researcher. It includes data generation, optimisations, troubleshooting, with equal doses of data presentation, literature searching, writing, editing, teaching, and other various forms of scientific communication. These skills also form a segment of a medical writer's skill set, which needs frequent adaptation and refining to render it effective. I would specifically highlight those precious proficiencies that PhDs could decorate and advise subtle actions that will make the transformation even smarter.

**In Germany, 28,147 PhD researchers wore their graduation hats in 2014. Do you know how many of them will eventually use the title "Professor" in front of their names? Most probably, no more than 130!**

### Skills of a PhD: indispensable for medical writing

Academia compels us to aim at a higher goal, publish X number of high impact articles and establish a lab. We neglect to focus on the smaller victories we achieve along this tough journey. We do not celebrate our first lab meeting, we overlook the dexterity in maintaining an up-to-date lab book, the red-linked first manuscript draft always drains our energy, and the nagging peer reviewer fuels nightmares. We ignore the enormous set of soft skills we gain from all these episodes. I try here to discern those skills that are essential for the transformation of an academic into a medical writer (Figure 1).

#### 1. Scientific communication

Communication forms the nucleus of a PhD's life. We need to communicate every day, orally or in a written form; this key feature constitutes a hefty chunk of the PhD curriculum. In fact, the importance of communication began when applying for your PhD programme.

**The world outside academia needs your expertise. There are several areas in industry where PhDs can shine without having any prior industry experiences.**

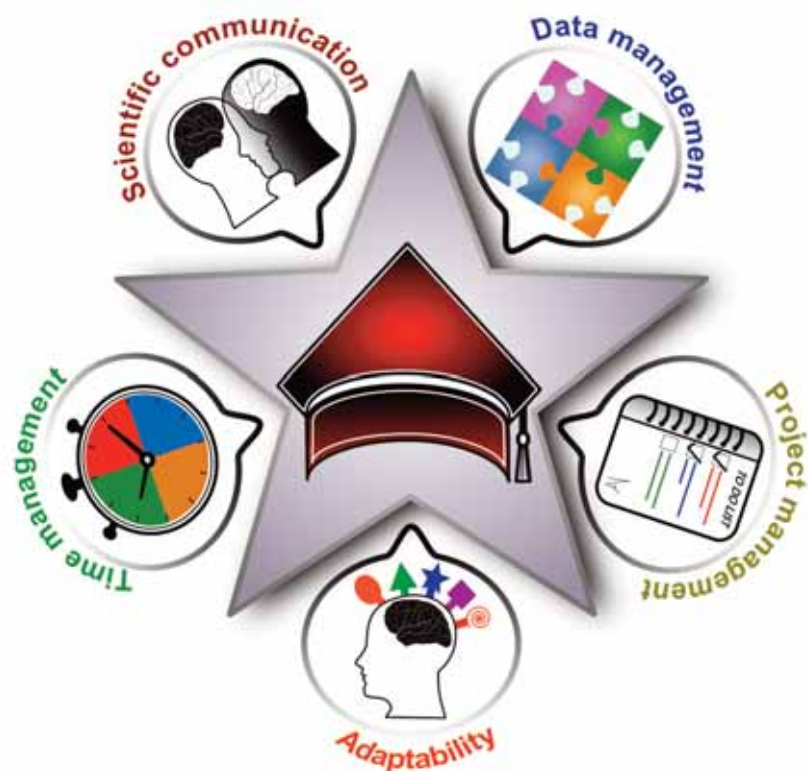


Figure 1. The skills owned by the PhDs, indispensable for a medical writer

You meticulously studied the lab’s research, aligned your skills to the existing projects, and wrote a spirited email to the principal investigator selling yourself. You ticked the box of scientific communication. The PhD training helped you to nurture it. Below are tasks a PhD does entailing scientific communication, the principal trait of a medical writer:

- Presenting in lab meetings and journal clubs
- Discussing research with colleagues, supervisors, or collaborators
- Presenting posters or talks in conferences
- Writing lab reports, literature reviews, and grant reports
- Writing articles, reviews, and thesis
- Peer-reviewing and editing scientific articles
- Communicating and negotiating with the interrogative peer-reviewers

**2. Data generation and integrity**

PhDs generate data, day in, day out. This activity not only helps churn out manuscripts but also teaches important skills related to data

security, data reproducibility, and supporting a hypothesis. This is a vital prerequisite to be a medical writer. Data management is in the spotlight of a medical writing affaire, where the remainder fails if the data are flawed or misrepresented.

**3. Project management**

PhDs are born project managers. They manage multiple projects laterally, ensuring a sound beginning coupled with a productive completion.

A successful project manager requires identification of achievable goals to be accomplished within a realistic time frame. This requires proper prioritisation and rectification. PhDs proudly take on these responsibilities. But how? A few tips are given below.

- Maintain an up-to-date lab notebook
- Manage to-do lists for the day, week, month, and year
- Optimise and troubleshoot experiments
- Write grant proposals and annual grant reports

Academia compels us to aim at a higher goal, publish X number of high impact articles and establish a lab. We neglect to focus on the smaller victories we achieve along this tough journey.

- Manage budget, reduce lab costs
  - Organise a conference or an event
  - Envisage success
  - Develop leadership skills
  - Delegate tasks to the lab members
  - Build and nurture collaborations
  - Ensure timely completion of the PhD thesis
- These skills are indispensable for medical writers, whether managing internal projects or those of clients.

**4. Time and self-management**

Manage yourself before starting projects. PhDs can do this singlehandedly, with examples listed below.

- Function effectively under limited supervision
- Endure and overcome immense pressure
- Maintain tight deadlines in finishing projects, manuscripts

PhDs must plan ahead; the process starts while writing grant proposals, laying out the plan for the next 3 to 5 years. We foresee a future milestone and then plan the path accordingly. This skill is also highly essential for a medical writer.

**5. Adaptability**

“Adaptability is not imitation. It means power of resistance and assimilation.”

–Mahatma Gandhi

A PhD life oscillates between rewards and obstructions. The adaptable PhDs can easily evade roadblocks by identifying probable solutions and learning from the mistakes. They could run several projects in parallel but prioritise depending on their importance.

Adaptability doesn’t only help a PhD to succeed in the lab; PhDs are global citizens. A recent study showed 32% of researchers who earned their PhD in UK are relocating to a different country.<sup>7</sup> Being adaptable comes handy here and eases the process of settling down in a foreign environment amidst an unfamiliar culture.

This is one of the key features of medical writers. They always need to be on their toes, to mould themselves according to the requirements of an assignment. Jumping from one therapeutic area to another, developing different regulatory documents, summarising reports for different products – all these tasks need quick but efficient attention shifts. Hence, medical writers’ adaptability is required to be at its peak.

## Tips, tweaks, and tricks: Nurture the budding medical writer

The previous section summarised the hidden qualities that PhDs usually do not recognise in their curriculum although unconsciously they absorb these soft skills that ultimately could help them to build a career in medical writing. Now, it is time to steer you through a few practices that will make this journey even more enticing (Figure 2).

### 1. Go beyond your research genre

A research article is not your baby! The efforts of co-authors, editors, peer reviewers, copy editors, and proofreaders amalgamate to bring out the final product. You must grasp areas beyond your research field. A certain versatility is necessary for medical writers, as they need to handle varied areas depending on the requirements of the agency they work for or their client's demand. Medical writers take on client's data as their own and efficiently grab the crux of it.

PhDs could master these skills too and a few suggestions are provided below.

- **Journal clubs**

The paper you're presenting to the journal club discussion group belongs to you for the next 30 minutes. Own it! Show your peers why this story has created such a roar in the field. Do not forget to show the ways it could have been even worthier. This process would not only sharpen your communication skills or problem-solving attitude, but it will also teach you how to train yourself quickly on something foreign to you by living it.

- **Peer reviewing**

This important task is similar to journal clubs but gives you more authority and enriches your evaluative skills. This certainly helps you enhance your research objectivity and achieve a sense of prestige as perks. However, remember, you are undercover during the whole process, completely anonymous!

- **Blogs**

Now you can remove that cover. Unleash your knowledge about anything under the sun. This creates a win-win situation. On the one hand, you polish your writing skills and show your target audience what you are capable of, and on the other hand, you already start creating your client

base. Now, this is your baby! Show your resourcefulness and versatility. Initially, you can pick a subject that is close to your genre but capable of merging you with another close-knit area, e.g., a common research tool or technique.

### 2. Use social media for a good purpose

In this smartphone age, we are all dwelling in a virtual world, but ordinarily forget to use our presence smartly. Here are ways how you can make your existence in social media fruitful.

- **Be a storyteller**

Do not merely share your holiday pics! Spend some words describing your experience. Emphasise what you learnt in those moments. Never let the communicator in you stand still. Be attentive, and use any little info as a brick to build your future. For instance, the exotic coconut tree during your last vacation in the tropics could inspire you to write about the health benefits of this fruit. Link your blog posts to your Facebook or Snapchat accounts. Make the posts interactive enough, compelling viewers to leave comments and be curious about your next story.

- **Build your virtual network**

This can be a real treasure. Connect

with people using professional networking platforms like LinkedIn. Clean your house before you invite! Have a polished account before sending networking request. Your profile should be your virtual face, linking your past to your present, aspiring for a brighter future. Share interesting stories/articles, engaging a like-minded community. By doing this, you are grabbing the attention of existing medical writers who could function as future job referrals or potential employers.

- **Volunteering**

Lend a hand. Allotting a small part of your day to volunteering could open the door to a better future. A study discloses volunteers are 27% more likely to find a job in comparison to the non-volunteers.<sup>8</sup> The following tasks could definitely motivate the volunteer in a PhD.

**Be a storyteller.**  
Do not merely share your holiday pics! Spend some words describing your experience. Emphasise what you learnt in those moments. Never let the communicator in you stand still.

- Help your PhD advisor to organise a conference
- Volunteer as the student representative at the university career centre
- Write press releases and help manage social media accounts of the university
- Organise PhD retreats and career days to network and help people in the same boat



Figure 2. The tips, tweaks, and tricks to nurture the budding medical writer

- Be a member of the European Medical Writers Association (EMWA). First, you will get to learn all the nitty-gritty information about medical writing. Second, you can act as volunteer to support the ongoing initiatives and get your foot in the door. The gained experience enriches your CV and helps you be a part of an extensive network of medical writers and scientific communicators.

#### 4. Look for a mentor

“A mentor is someone who sees more talent and ability within you, than you see in yourself, and helps bring it out of you.”

– Bob Proctor



EMWA provides you the precious opportunity to network and communicate with medical writers from all over Europe. Attend an EMWA conference and build strong relationships; this could be the best platform to identify your future mentor.

Mentors will certainly inspire your personal and professional growth. Especially during the phases when the impostor syndrome creeps into the lives of the PhDs, the mentor’s encouragement works as a charm. Mentors identify your strengths and make them even stronger, and turn the weaknesses into your strengths. Find a mentor who is currently working as a medical writer and has extensive experience to guide you through the steps to achieve your goal.

EMWA provides you the precious opportunity to network and communicate with medical writers from all over Europe. Attend an EMWA conference and build strong relationships; this could be the best platform to identify your future mentor. Be proactive and show genuine enthusiasm before asking someone to mentor you. Create an affiliation of mutual knowledge and experience sharing. Try to give more than what you receive! Then you can take the proceedings forward by being a mentor.

### Conclusion

PhDs acquire certain skills during their study period mostly unconsciously. This article makes these skills conspicuous enough for the PhDs to realise that they are capable of leading a meaningful career in science even outside of academia.

Hey PhDs! The philosophy of “publish or perish” cannot be the sole standard to gauge your talent. You are smart enough to break the so-called dogma. Nevertheless, you need to find your niche as quickly as possible. My attempt here is to help you find your niche as a medical writer by highlighting the skills you already own and the ways you can invigorate the process even further.

### Acknowledgements

I would like to thank Dr Sneha Patra for the immense assistance in creating the figures.

### Disclaimers

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

### Conflicts of interest

The author is employed by the Philipps University Marburg. The views and opinions shared in this article are those of author alone and do not necessarily reflect those of his employer.

### References

1. OECD (2016), OECD Science, Technology and Innovation Outlook 2016. OECD Publishing, Paris; 2016.
2. The Scientific Century: securing our future prosperity. RS Policy document 02/10 The Royal Society; 2010.
3. OECD (2017), Gross domestic spending on R&D (indicator); 2017.
4. Weir K. Feel like a fraud? [Cited 2013 November] gradPSYCH Magazine, American psychological association. Available from: <http://www.apa.org/gradpsych/2013/11/fraud.aspx>.
5. Levecque K, Anseel F, Beuckelaer AD, Heyden JVD, Gisle L. Work organization and mental health problems in PhD students. Res Policy. 2017;46(4);868–79.
6. Why PhDs Are More Valuable Than Other Job Candidates [Cited 2017 April] LinkedIn article, Available from: <https://www.linkedin.com/pulse/why-phds-more-valuable-than-other-job-candidates-sorbara-phd/>.
7. Bohannon J, Doran K. Data from: Introducing ORCID. Science. 2017; 356(6339); 691–2.
8. Spera C, Ghertner R, Nerino A, DiTommaso A. Volunteering as a Pathway to Employment: Does Volunteering Increase Odds of Finding a Job for the Out of Work? Corporation for National and Community Service, Office of Research and Evaluation: Washington, DC, 2013.

### Author information

**Somsuvro Basu**, PhD, is a molecular cell biologist by training. He has more than 8 years’ research experience spanning from parasitology to human mitochondrial biology. He is pursuing his postdoctoral research at the Philipps University Marburg, Germany, and gearing up to be a medical writer. He is proudly associated with the EMWA social media team.

# News from the EMA

## SECTION EDITORS



Section Editor:

**Anuradha Alahari**

Anuradha.Alahari@parexel.com



EMA contact:

**Monika Benstetter**

press@ema.europa.eu

The articles included in this section are a selection from the European Medicines Agency's News and Press Release archive from October 2017 to December 2017. More information can be found on the Agency's website: <http://www.ema.europa.eu/>

## New action plan to foster development of advanced therapies

**October 20, 2017** — The European Commission's Directorate-General for Health and Food Safety (DG SANTE) and the European Medicines Agency (EMA) have published today a joint action plan to foster the development of advanced therapy medicinal products (ATMPs). The main aim is to streamline procedures and better address the specific requirements of ATMP developers.

ATMPs are medicines for human use that are based on genes or cells. These therapies offer ground-breaking new opportunities for the treatment of disease and injury. They are particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate. ATMPs can be classified into four main groups: gene therapy medicinal products, somatic cell therapy medicinal products, tissue engineered medicinal products and combined ATMPs. EMA has received 18 marketing authorisation applications since the ATMP regulation came into force in 2009. Nine products have been approved.

The Agency's Committee for Advanced Therapies (CAT) plays a central role in the scientific assessment of ATMPs, as it provides the expertise needed to evaluate these medicines. Other initiatives include European Commission research programmes, the innovation offices in the national competent authorities and EMA's PRIME scheme.

At international level, a regular forum for dialogue has been set up with the United States Food and Drug Administration (FDA), Health Canada and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) to share experience on ATMPs. EMA and the CAT also contribute to the cell therapy group and gene therapy group of the International Pharma-



ceutical Regulators' Forum (IPRF).

DG SANTE and EMA, in collaboration with the Member States' competent authorities, are working on some initiatives to support the development and authorisation of high quality, safe and effective ATMPs. The plan published today contains 19 actions in different key areas. Some of the actions are already in place, others are new. Actions were also informed by the ideas collected during a multi-stakeholder workshop hosted by EMA on May 27, 2016. The workshop aimed to explore solutions to identified challenges in the development of ATMPs. Topics discussed ranged from the need for early interaction and guidance from regulators, to more transparency and information sharing, greater harmonisation between Member States in various aspects of ATMP regulation and measures to tackle inequalities in patient access to ATMP treatments.

Examples of forthcoming actions in the plan include:

- European Commission guideline on good manufacturing practice for ATMPs, to reduce the administrative burden and adapt the manufacturing requirements to the specific characteristics of ATMPs;
- Initiation of dialogue with national competent authorities to address the interplay between the legislation on genetically modified organisms (GMO) and on medicines, to reduce discrepancies across the European Union (EU) regarding the application of GMO rules;
- New EMA scientific guidelines on ATMPs, including investigational ATMPs, to clarify regulatory expectations;
- Continuous awareness and training sessions organised by EMA for the EU network on ATMP-related topics.

DG SANTE and EMA will continue monitoring the field and propose further initiatives as appropriate.

## How to develop vaccines and medicines that prevent and treat respiratory syncytial virus infection

**October 30, 2017** – Respiratory syncytial virus (RSV) is a common respiratory virus that usually causes mild, cold-like symptoms. Most people recover within one to two weeks, but RSV can be serious, especially in infants and older adults. It is the most common cause of lower respiratory tract infections, such as bronchiolitis (inflammation of the small airways in the lungs) and pneumonia (infection of the lungs), in newborn babies and young infants. RSV is also a significant cause of respiratory illness in the elderly. Several medicines are currently under development for RSV disease, for which there is no specific vaccine and only a few treatments available.

The EMA has released a new guideline to support and facilitate the development of vaccines and medicines to prevent and treat infections caused by RSV for a six-month public consultation. Stakeholders are invited to send their comments by April 30, 2018, to [vwp@ema.europa.eu](mailto:vwp@ema.europa.eu) using the template provided in the guideline.

EMA's new draft guideline provides advice for medicine developers on how they can best develop safe and effective vaccines and monoclonal antibodies to prevent RSV disease, and direct-acting antiviral agents (DAAs) to treat it. The guideline focuses on assessment of safety and efficacy of vaccines and medicines in

people most likely to develop RSV lower respiratory tract infection and severe RSV disease, including newborn babies (0 to 27 days), infants (28 days to 11 months), toddlers (12 to 23 months), older children who are likely to develop severe RSV disease and people aged over 65 years. It also addresses the vaccination of pregnant women with the aim of preventing RSV disease in their babies, once they are born.

Other areas for which guidance is provided include diverse aspects such as study design, how to assess the efficacy of a vaccine in different scenarios, and the selection of the recommended dose regimen for medicines.

## New medicine for multiple sclerosis

**November 10, 2017** – The EMA has recommended granting a marketing authorisation in the EU for Ocrevus (ocrelizumab) for the treatment of adult patients with relapsing multiple sclerosis (RMS) and early primary progressive multiple sclerosis (PPMS). There are currently no disease-modifying therapies available for this particular form of multiple sclerosis (MS) so there is a great medical need for treatment of such a relentless, seriously debilitating disease. Ocrevus is first medicine to receive positive opinion for treatment of patients with early stage of PPMS.

MS is a condition that affects the brain and/or spinal cord, causing a wide range of potential symptoms, including problems with vision, arm or leg movement, sensation or balance. It occurs more frequently in women than men and is among the most common causes of neurological disability in young adults. In the majority of patients (around 85%), MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery. For the approximately 10% of patients with PPMS the disease is characterised by worsening neurologic function from the onset of symptoms, without early relapses or remissions.

The recommendation from EMA's Committee for Medicinal Products for Human Use (CHMP) is based on data from three pivotal Phase III clinical trials in 1423 patients with MS (two in RMS and one in PPMS patients). Treatment with Ocrevus significantly reduced the annualised relapse rate by 46.4% at 96 weeks compared with interferon beta-1a treatment in



patients with RMS. For patients with PPMS, treatment with Ocrevus led to a 24% reduction in the risk of 12-week confirmed disability progression compared with placebo. Data from the clinical trial in PPMS indicate that patients in the early stage of disease benefit more from the medicine. More investigation is needed to better understand how beneficial Ocrevus might be in the more advanced stages of the disease.

The most common adverse reactions observed with Ocrevus are infusion-related reactions and infections. The CHMP therefore recommended that Ocrevus treatment should be initiated and supervised by an experienced healthcare professional with access to appropri-

ate medical support to manage severe reactions.

The opinion adopted by the CHMP at its November 2017 meeting is an intermediary step on Ocrevus' 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. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.

The applicant for Ocrevus is Roche Registration Limited.

## EMA to relocate to Amsterdam

**November 20, 2017** – The EMA will relocate to Amsterdam. This decision was taken today by the EU 27 Member States in the margins of the General Affairs Council (Art. 50). The EMA has been based in London, since it was established in 1995. It currently employs nearly 900 staff members at its headquarters in Canary Wharf, London. The Agency now has to prepare for the move and take up its operations in Amsterdam on March 30, 2019, at the latest.

EMA's relocation is due to the UK's decision to withdraw from the EU. Amsterdam was one of 19 offers to host EMA submitted by the Member States at the end of July 2017. The decision on EMA's new location follows an assessment of the bids by the European Commission and EMA.

Effective collaboration between EMA and the Netherlands on the basis of the



commitments made in its offer to host EMA is essential to ensure a successful move and the continuation of EMA's operations with minimal disruption. EMA and the Netherlands will kick start their collaboration by establishing a joint governance structure to steer and oversee the relocation project. 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. In early December 2017, the Agency made available a monitoring chart on its website that allows tracking the progress made.

## First guidance on monoclonal antibodies for use in animals



**December 11, 2017** – The EMA's Committee for Medicinal Products for Veterinary Use (CVMP) has approved the first ever guidance at EU level for monoclonal antibody therapies for veterinary use. The guidance was prepared by the CVMP's Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT) in the form of a question-and-answer document.

The guidance relates to particularities of

monoclonal antibodies for veterinary use, quality control for potential contaminants, stability testing, reproductive safety studies and data to address potential for indirect adverse effects.

Monoclonal antibodies are immune proteins that recognise and bind to a specific target protein, and have not been used in veterinary medicines until recently. In human medicine, these therapies have been authorised for many

years for use against cancer and diseases affecting the immune system, such as rheumatoid arthritis. Therapies that are new to veterinary medicine face particular challenges due to a lack of regulatory guidance. Despite these challenges, the first veterinary medicine containing a monoclonal antibody was recommended for approval by the CVMP in February 2017.

Veterinary novel therapies refer to therapies that are either genuinely new, or new only to the veterinary domain, although well known in the context of human medicines. Interest and research activities into veterinary novel therapies have increased over the last few years. The CVMP identified monoclonal antibodies as one of the priority areas that would benefit from specific guidance, following a review of relevant scientific evidence, such as published literature, available guidance on such medicines for human use, experience gained by the CVMP through scientific advice and public consultations.

ADVENT brings together broad knowledge and expertise on the scientific aspects of veterinary medicines and their regulation. The group makes use of additional expertise from across the European network. It was set up by the CVMP to prepare general guidance on the requirements for authorisation of novel veterinary medicines. In this context, the group also prepares guidance on other types of novel therapies. For example, guidance on three different aspects of veterinary stem cell therapies was published earlier this year.



## Modified-release paracetamol-containing products to be suspended from EU market: Recommendation endorsed due to the difficulty in managing overdose

**December 15, 2017** – The CMDh, which is a medicines regulatory body representing the EU Member States, Iceland, Liechtenstein, and Norway, has endorsed an EMA recommendation to suspend marketing of modified- or prolonged-release products containing paracetamol (designed to release paracetamol slowly over a longer period than the usual immediate-release products). The recommendation was made by the Agency's experts in medicines safety, the Pharmacovigilance Risk Assessment Committee (PRAC). As the CMDh position was adopted by majority vote, the CMDh position will now be sent to the European Commission, which will take an EU-wide legally binding decision.

CMDh agreed with the Agency's advice that the advantages of a longer-acting product did not outweigh the complications of managing an overdose of the medicine, since the treatment procedures for immediate-release products are not appropriate for modified-release paracetamol. In many cases, it may not be known whether an overdose of paracetamol involves immediate-release or modified-release products, making it difficult to decide how the overdose should be managed.

CMDh noted the PRAC conclusion that practical measures to sufficiently reduce the risk to patients had

not been identified. Furthermore, it had not proved possible to agree a feasible and standardised way to adapt the management of overdose across the EU to cover both immediate- and modified-release paracetamol products. The CMDh therefore endorsed the PRAC recommendation that the marketing authorisations for medicines containing modified-release paracetamol, alone or combined with the opioid medicine, tramadol, should be suspended.

The medicines will remain suspended unless the companies that hold the marketing authorisations can provide evidence of appropriate and practical EU-wide measures to help prevent overdose with these products and adequately reduce its risks. Immediate-release paracetamol products, which are not affected by this review, will continue to be available as before.

The Agency's recommendations are based on a review of available data including a retrospective pharmacokinetic and clinical analysis of 53 cases of acute overdose with modified-release paracetamol by the Swedish Poison Information Centre, which found that the standard treatment protocol utilising solely the Rumack-Matthew nomogram (or variations thereof) based on conventional paracetamol formulations may not be effective for overdoses with modified-release paracetamol formulations. The maximum plasma concentration may occur later, and high concentrations, in particular after large doses, may persist for several days. The usual protocols of sampling and treatment regimens used in the management of overdose with immediate-release formulations are therefore not adequate.

These results confirm a similar Australian case series.



# Save the date

The 47th EMWA Conference in  
**Warsaw, Poland**  
November 8–10, 2018

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

## A new medicine for the treatment of X-linked hypophosphataemia, a rare bone disease: Recommended for conditional approval

**December 15, 2017** – The EMA’s CHMP has recommended granting a conditional marketing authorisation in the EU for Crysvida (burosumab), a medicine for the treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

XLH is an inherited disorder characterised by low levels of phosphate in the blood. The phosphate is abnormally processed in the kidneys, which causes a loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones (rickets). In most cases, the signs and symptoms of hereditary hypophosphataemic rickets begin in early childhood. Characteristic features include bowed or bent legs, short stature, bone pain, and severe dental pain.

The CHMP recommended conditional approval for the medicine. This is one of EU’s regulatory mechanisms to facilitate early access to medicines that fulfil unmet medical need. Conditional approval allows the Agency to recommend a medicine for marketing authorisation in the interest of public health where the benefit of its immediate availability to patients outweighs the risk inherent in the fact that additional data are still required.

There is currently no authorised medicine available to treat this rare, serious, chronic and debilitating disease. Most children with XLH receive conventional therapy

consisting of multiple daily doses of oral phosphate and active vitamin D analogues. The benefits of Crysvida are its ability to reduce the loss of phosphate, improve abnormally low serum phosphate concentrations and other metabolic changes, and to reduce the severity of rickets as shown in X-rays.

The CHMP’s recommendation is based on two phase II studies. The main study was conducted on 53 children aged 5-12 years. Children treated with Crysvida experienced an improvement in their phosphate level and in the reabsorption of phosphate in their kidneys as well as radiographic improvement of rickets. In the second study of 13 patients age 1 to 4 years old receiving Crysvida, the response was similar than in children in the main study. On this basis, the CHMP considered that efficacy results from age group 5-12 years can be extrapolated to ages 1 to 4 years old. The most common adverse reactions observed with Crysvida were injection site reactions, headache, and pain in extremities.

As part of the conditional marketing authorisation, the applicant is required to complete three ongoing studies to further investigate the safety and efficacy of the

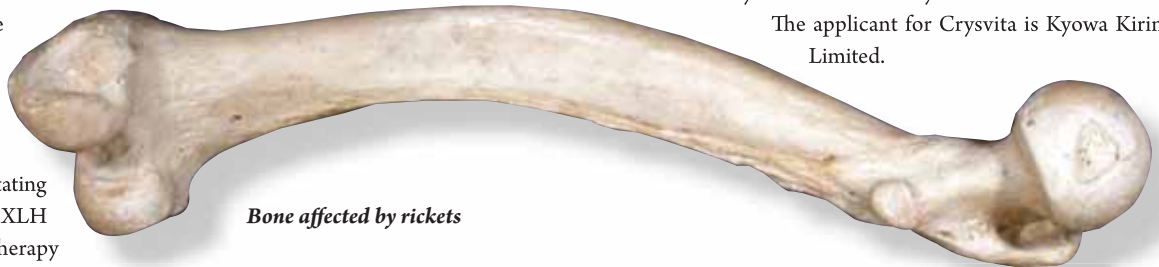
medicine. The data from all three studies are planned to be submitted by 2020.

The CHMP recommended that Crysvida will be prescribed by physicians experienced in the management of patients with metabolic bone diseases.

Because XLH is rare, Crysvida received an orphan designation from the Committee for Orphan Medicinal Products (COMP) in October 2015. As always at time of approval, this orphan designation will now be reviewed to determine whether the information available to date allows maintaining burosumab’s orphan status and granting this medicine ten years of market exclusivity.

The opinion adopted by the CHMP at its December 2017 meeting is an intermediary step on Crysvida’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. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.

The applicant for Crysvida is Kyowa Kirin Limited.



# Save the date

The 46th EMWA Conference in  
**Barcelona, Spain**  
May 1-5, 2018  
Featuring a symposium on medical devices

# Medical Communications

## Editorial

Dear all,

In this first issue of 2018, I'm delighted to introduce an excellent article from one of EMWA's newest Workshop Leaders, John Dixon. Although John is new to teaching at EMWA, he's extremely experienced in his field – or, more correctly, fields! John qualified in medicine and initially trained as a surgeon before becoming a GP. Since 2003, John has completed an MBA and spent 5 years as Director of Medical Communications at InterComm International Ltd, becoming a healthcare communications consultant and trainer in scientific writing in 2013.

John shares all of our frustration at poorly

written and presented articles, and he brings his formidable knowledge and experience to bear on this topic in his article for *Medical Writing*. With characteristic humour and (as would be expected) great clarity, John explains that biomedical research writing is becoming increasingly difficult to read and understand, suggesting a review of the reasons for this as he does so. It is ironic that, with the Industry push towards open access and transparency, the information available is becoming increasingly difficult for readers to understand! However, John assures us that this is not a lost cause and suggests some tools that medical writers (and others) can use to help us all to think more about readability and how we write.

## SECTION EDITOR



Lisa Chamberlain James

[lisa@trilogywriting.com](mailto:lisa@trilogywriting.com)

This issue's article is a fascinating read and certainly reminded me of some of the reasons why readability is so crucial. I particularly liked John's cartoon, and I look forward to further thoughts and articles from him. Rest assured – I will make sure that I “shake off the ball and chain of traditional scientific writing”!

Bestest,

Lisa

## Readability of biomedical research articles: Where are we now, and how can we move on?

### Readable biomedical research articles – an oxymoron?

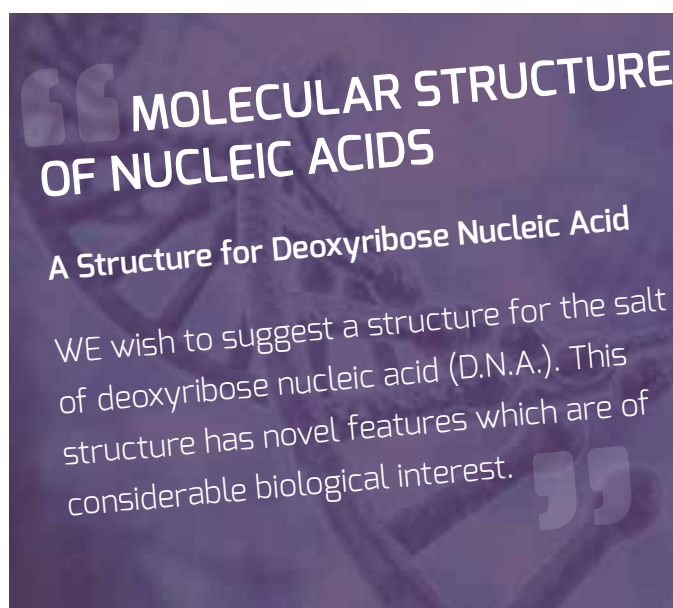
How often do we glide through a biomedical research article and think “this is well written”? Not often. Long gone is the time of highly readable articles such as Watson and Crick's classic 1953 paper on the structure of DNA.<sup>1</sup> I've spent years having to reread original articles because I'm struggling to understand what's going on. I used to think it was me. Perhaps this is partly true, and science is getting more complicated and sub-specialised. But authors of research articles do have something to answer for, even though it may not be their fault. We scientists have become writers without learning how to write readable prose. Instead, we copy what we read in original articles, thinking this is good style. We use intelligent-sounding text with long, complex sentences and scientific jargon. This style is deeply rooted – a ‘culture’ – and any challenge can meet with resistance. Indeed, after a recent workshop I delivered on effective scientific writing, a doctoral student came up to me. She said [*upset tone*]: “You mean to tell me that everything I've been taught about scientific writing is wrong! Well...”. Either through reader assessment or using readability formulas, the

conclusion is the same. Biomedical research articles are usually hard to read – as hard as legal contracts.

### Growing inaccessibility of science despite open access

Worryingly, this situation is getting worse. Shown in a recent study of 700,000 abstracts in over 100 journals from the biomedical and life sciences from 1881 to 2015, articles have become progressively less readable.<sup>2</sup> True, science is getting more complex. But the authors associated this decline with an increase in the use of general scientific jargon (e.g. *mediated, paradigm, attenuated*) – and not, as one might expect, with discipline-specific words (e.g. *theophylline, post-synaptic, mutagenesis*).

Donald Hayes (sociologist) described this trend as a “growing inaccessibility” of science.<sup>3</sup> So, articles are becoming even less readable! Yet we now live in the era of open access – improving access to research articles for everyone. Can anyone see a problem here?



## Declining readability of our most trusted scientific resource, but who cares?

Here's another problem. Peer-reviewed articles are the most trusted source of scientific information for everyone from academic scientists to the general public – an important argument supporting the need for open access to *readable* manuscripts.<sup>4</sup> Peter Suber (philosopher) reminded us of a “patronising” opinion held by some that “lay people don't care to read research literature and wouldn't understand it if they tried.”<sup>5</sup> Countering this view, he advised us to read the moving account of a mother (without a scientific background) whose children had a rare and poorly documented genetic abnormality. She described her desperate attempts to *access* and *understand* any information to enable her to communicate with doctors and to help her children.<sup>6</sup> Only peer-reviewed articles were of any help to her – and back then in 2005, most were protected by journal paywalls. Completing the picture, academic staff and postgraduates of science also benefit from articles being more readable.<sup>7</sup> So, whether lay public or scientific specialists, we all care. We all need open access to *readable* manuscripts, the most trusted source of scientific information.

### “– no more research on the topic is needed”: We need solutions!

Despite Hayes' advice back in 1994, yet another article (in the *BMJ*, 2002) illustrated how medical articles published in major journals such as the *BMJ* and *JAMA* were “extremely difficult to read.”<sup>8</sup> Mark Hochhauser (a readability consultant) commented on this study in a subsequent letter to the *BMJ*. He advised that “no more research on the topic is needed”<sup>9</sup> because researchers will continue to reach the same conclusion.<sup>9</sup> He felt that readability studies have no influence on “physicians-researchers-writers”.

Research continues. However, having inevitably come to the same conclusion, some authors do suggest ways forward. In 2017, a study in *The Lancet* illustrated the plight of the modern e-patient. Assuming patients with chronic disease (e.g. diabetes) want to read online medical papers about their condition, many will be disappointed. Smith and colleagues found that abstracts about diabetes and sport were written at a readability level beyond such an audience.<sup>10</sup> They recommended increased use of lay summaries,

and some journals already provide these (e.g. *BMJ*, *PLOS Medicine*, Nature Partner Journals).

A lay summary is just one of many avenues available to help non-scientists understand scientific research. Many non-scientists rely on science journalism, blogs, press releases and social media. Together, these pathways to help interpret and disseminate scientific knowledge represent a “science media ecosystem”.<sup>11</sup> Wikipedia increasingly acts as an “amplifier” for open access literature.<sup>12</sup> Perhaps patients with medical knowledge and Web 2.0 skills – patient rapporteurs – will become important intermediaries to help translate original research into understandable online material for e-patients.<sup>10</sup>

The science media ecosystem and intermediaries help people understand and interpret science. Arguably though, these are not good solutions. Indeed, in 2003, Jonathan Knight (physicist) quoted the editor-in-chief of *Science*, who called lay summaries and weblinks “Band-Aids” to solving the problem.<sup>13</sup> Knight himself suggested these were only “bit-part solutions”. They don't get to the heart of the matter – the readability of the articles themselves. So, even though discipline-specific and technical words are mostly unavoidable, can we do anything to improve the readability of original articles? Or is it a lost cause?

### The heart of the matter: Improving readability of original articles

In 2007, John Ludbrook (medical researcher and surgeon) reviewed ways to improve the readability of biomedical journals.<sup>14</sup> He advocated better teaching of writing skills at school and better supervision of postgraduate students. Is this possible? He recommended that postgraduates and their supervisors should read books on scientific writing. Good idea. So, let's not forget some great articles in *Medical Writing* – see for example the March 2017 edition on the topic of “writing better”.

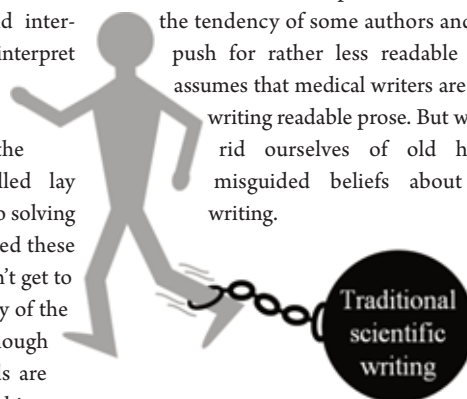
Ludbrook encouraged university courses on writing skills, although he thought that students didn't make enough use of these. In my experience, postgraduate students are keen to attend such courses, but these courses are in short supply. Further, well-intentioned students may wish to attend a course, only to be asked at the eleventh hour to devote their time to something others consider more pressing. *Truly*

protected time would be nice.

Ludbrook suggested that editorial staff of biomedical journals could play a more active part in improving text before publication. Larger journals do make small improvements,<sup>15</sup> but smaller journals are usually unable to handle technical editing. Perhaps journals should offer an award for the most readable paper of the year.<sup>13</sup>

Closer to home, Ludbrook and others have recommended that both authors and journals employ professional science editors<sup>13</sup> – also known as medical writers. We medical writers have an important role in preparing manuscripts that are as readable as possible – that is, despite

the tendency of some authors and clients to push for rather less readable text! This assumes that medical writers are masters of writing readable prose. But we too must rid ourselves of old habits and misguided beliefs about scientific writing.



### Readability formulas and online tools

Ludbrook and others have suggested that authors could use readability formulas.<sup>2,16</sup> Some actively recommend formulas, but Ludbrook thought that this was unlikely to help. I also think such tools are unlikely to help physicians–researchers–writers when they are in the midst of writing up new research. However, I think readability formulas and other tools can help – *when in the right hands and used as learning aids*. I suggest that the “right hands” are university graduates undertaking their first scientific research, and medical writers.

When running a spelling and grammar check on any document in Microsoft Word, anyone can apply two of these readability formulas: the Flesch Reading Ease and Flesch–Kincaid Grade Level formulas. They give a quantitative measure of readability. However, they were not designed to assess the readability of biomedical research articles, despite used widely for this purpose. Online readability tools include the Hemingway Editor and Readable.IO.<sup>17,18</sup> These provide a visual analysis of text readability and make it easy to find problem sentences and words.

Medical writers should take time to experiment with these formulas and tools and use them to assess the readability of a piece of their own writing. This gives a practical feel for some of the important ways to improve readability. These include using shorter sentences; using shorter, non-technical words to replace longer words; removing unnecessary words such as adverbs; and balancing the use of the active and passive voice. Like golfers experimenting with their swing on the practice ground, playing around with readability formulas and tools can be more fun than reading books on the subject. Perhaps budding physicians-researchers-writers could benefit from exploring these tools at leisure, away from the immediate pressure of deadlines. Postgraduates and medical writers often love exploring these tools, enjoy the discussion they provoke, and indeed some tell me they continue to use them during the day job.

## Conclusions: Hard truths but hopefully not a lost cause!

Many biomedical research articles are hard to read. There are bit-part solutions to help interpret research articles. But we need more-readable articles, not least because of open access and our overriding trust in original articles. Old writing habits die hard. Learning new writing skills is hard. However, I suggest there are some useful tools in the box to explore and enjoy using. Authors of articles like this sometimes end with a boast about the article's readability score. I'll deviate and let you look at a colourful analysis of some of this article using the Hemingway Editor (Figure 1). Satisfactory text is not highlighted!

## Acknowledgements

The image of a person with a ball and chain was adapted from an original image at <https://www.dreamstime.com/stock-photography-man-dragging-chains-big-ball-debt-burden-concept-image34286972>.

## References

1. Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature*. 1953;171:737–8.
2. Plavén-Sigra P, Matheson GJ, Schiffler BC, Thompson WH. The readability of scientific texts is decreasing over time. *eLife*. 2017;6:e27725.

The screenshot shows the Hemingway Editor interface. The main text area contains a paragraph about biomedical research readability. The text is highlighted in yellow and green. The right sidebar shows the readability score as 'Grade 8' and 'Good'. Below the score, it lists 'Words: 215' and 'Show More +'. There are five colored boxes with icons and text describing issues: 1. Adverbs (blue), 2. Use of passive voice (green), 3. A phrase with a simpler alternative (purple), 4. 17 sentences are hard to read (yellow), and 5. 17 sentences are very hard to read (red).

Figure 1. Analysis of the first paragraph of this article using Hemingway Editor

3. Hayes DP. The growing inaccessibility of science. *Nature*. 1992;356:739–40.
4. Wilson MJ, Ramey TL, Donaldson MR, Germain RR, Perkin EK. Communicating science: Sending the right message to the right audience. *FACETS*. 2016;1:127–37.
5. Suber P. *Open Access*. Cambridge, MA: MIT Press; 2012.
6. Terry S. In the public interest. *Open access*. *College & Research Libraries News*. 2005;66(7):522–5.
7. Hartley J. Three ways to improve the clarity of journal abstracts. *Brit J Educ Psychol*. 1994;64:331–43.
8. Weeks WB, Wallace AE. Readability of British and American medical prose at the start of the 21st century. *BMJ*. 2002;325:1451–2.
9. Hochhauser M. Readability of British and American medical prose. Why are unreadable articles still being written? *BMJ*. 2003;326:711.
10. Smith K, Buchanan P, McDonald P. How easy is it for a lay audience to read medical journals? A survey of the readability scores of a sample of research papers on diabetes. *The Lancet*. 2017;390:S82.
11. Kuehne LM, Olden JD. Opinion: Lay summaries needed to enhance science communication. *P Natl Acad Sci USA*. 2015;112:3585–6.
12. Teplitskiy M, Lu G, Duede E. Amplifying the impact of open access: Wikipedia and the diffusion of science. *J Assoc Inf Sci Tech*. 2017;68:2116–27.
13. Knight J. Scientific literacy: Clear as mud. *Nature*. 2003;423:376–8.
14. Ludbrook J. Writing intelligible English prose for biomedical journals. *Clin Exp Pharmacol P*. 2007;34:508–14
15. Wager E, Middleton P. Effects of technical editing in biomedical journals: a systematic review. *JAMA*. 2002;287:2821–4.
16. Hall JC. The readability of original articles in surgical journals. *ANZ J Surg*. 2006;76:68–70.
17. Readable.IO. 2018. [cited 2018 Jan 02]. Available from: <https://readable.io/>.
18. Hemingway Editor. 2018. [cited 2018 Jan 02]. Available from: <http://www.hemingwayapp.com/>.

**John Dixon**

Director of Medical Communications  
InterComm International Ltd  
[john.dixon@libramedmarketing.co.uk](mailto:john.dixon@libramedmarketing.co.uk)

# 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



**Hervé Maisonneuve**  
herve@h2mw.eu

## A proposal to change the default *P*-value threshold

The one sentence summary of a paper signed by 72 statisticians was: “We propose to change the default *P*-value threshold for statistical significance for claims of new discoveries from 0.05 to 0.005”.<sup>1</sup> The proposal is straightforward, but it must be correctly understood, as it targets new discoveries.

*This simple step would immediately improve the reproducibility of scientific research in many fields. Results that would currently be called “significant” but do not meet the new threshold should instead be called ‘suggestive’. They clarified that “We restrict our recommendation to claims of discovery of new effects. We do not address the appropriate threshold for confirmatory or contradictory replications of existing claims. We also restrict our recommendation to*

*studies that conduct null hypothesis significance tests. We have diverse views about how best to improve reproducibility, and many of us believe that other ways of summarising the data, such as Bayes factors or other posterior summaries based on clearly articulated model assumptions, are preferable to *P*-values.*

Such a proposal could favour large studies and concentrate funding to few research groups.

In another report, *Nature* asked five influential statisticians their views on the role of statistics in poor reproducibility of results and to each recommend one change to improve interpretation of data.<sup>2</sup> The five answers concerned the researchers’ practices rather than the use of statistics and can be summarised as:

“Adjust for human cognition.”

– Jeff Leek, Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland

“Abandon statistical significance.”

– Blakeley B. McShane, Northwestern University, Evanston, Illinois, and Andrew Gelman, Columbia University, New York

“State false-positive risk, too.”

– David Colquhoun, University College London

“Share analysis plans and results.”

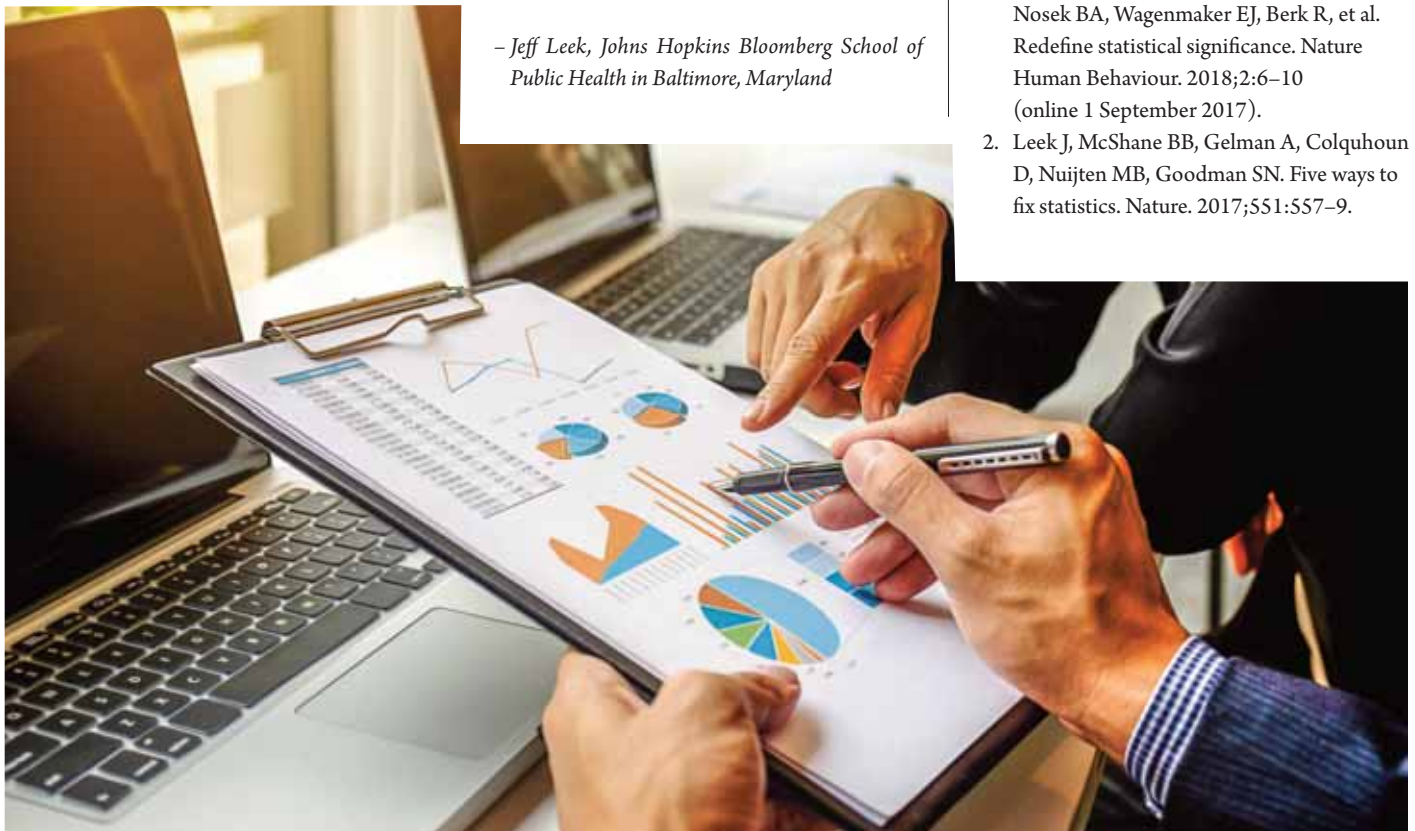
– Michèle B. Nuijten, Tilburg University, the Netherlands

“Change norms from within.”

– Steven Goodman, Stanford University, California

## References

1. Benjamin DJ, Berger JO, Johannesson M, Nosek BA, Wagenmaker EJ, Berk R, et al. Redefine statistical significance. *Nature Human Behaviour*. 2018;2:6–10 (online 1 September 2017).
2. Leek J, McShane BB, Gelman A, Colquhoun D, Nuijten MB, Goodman SN. Five ways to fix statistics. *Nature*. 2017;551:557–9.



## Guidelines for the content of statistical analysis plans in clinical trials

A group of experts has prepared, tested, and published a list of 55 items/sub-items as guidance for preparing a Statistical Analysis Plan (SAP) for clinical trials.<sup>1</sup> The researchers conducted a survey of current practice across trial units registered with the UK Clinical Research Collaboration and used a Delphi survey to collect information from 73 invited participants including statisticians, guidelines authors, and journal editors. This was followed by a consensus meeting. No existing guidance for SAP content was identified in their literature search or contacts with funders and regulators. The SAP is not a stand-alone document but rather should be read in conjunction with the clinical trial protocol; the protocol should be consistent with the principles of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement. According to ICH E9 (Statistical Principles for Clinical Trials), a



SAP “contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data”.

The 55 items/sub-items are listed under six sections: Title and Trial Registration; Introduction; Study Methods; Statistical Principles; Trial Population; and Analysis. The supplementary online content has additional information and examples for each item. Some journals,

including *JAMA*, require the SAP to be submitted along with the report of a clinical trial for use within the peer-review process.<sup>2</sup>

### References

1. Gamble C, Krishan A, Stocken D, Lewis S, Juszcak E, Doré C, et al. Guidelines for the content of statistical analysis plans in clinical trials. *JAMA*. 2017;318:2337–43.
2. DeMets DL, Cook TD, Buhr KA. Guidelines for statistical analysis plans. *JAMA*. 2017;318:2301–3.

## Authorship policies in an age of large research teams

A five-page editorial authored by *JAMA* editors explains their policy for maintaining integrity of authorship in team science.<sup>1</sup> Their concern is that as science has become increasingly collaborative, it is becoming more common for papers to have hundreds or even thousands of listed authors. They gave examples of papers on the sequencing of the human genome with 270 authors and 240 listed as collaborators. In their editorial, they have reproduced the *JAMA* Network journals authorship form. Authors must comply with the four ICMJE (International Committee of Medical Journal Editors) criteria. Individuals who do not meet authorship criteria but who have made important substantive contributions to the work should be acknowledged for their contributions and can be listed as collaborators. The main headings of the editorial are: author and research group designations; other authorship considerations (author contributions, shared author responsibilities, changes in authorship, resolving disagreements among authors). The following terms and definitions are listed:

- **Contributor:** Anyone, such as an author, a collaborator, or any other who has assisted or contributed in a meaningful way to the work.
- **Author:** A type of contributor who has

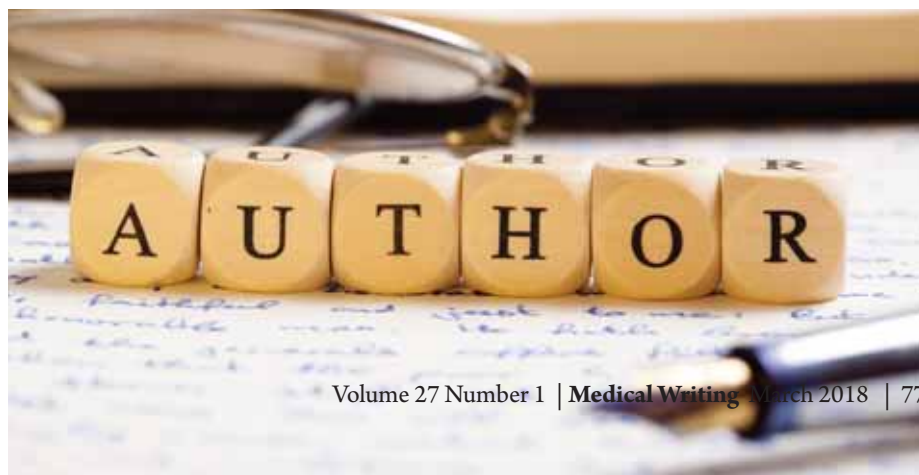
participated sufficiently in the work to take public responsibility for the content, either all of the work or an important part of it, and meets defined criteria for authorship. Identification of authorship in a manuscript and published article can appear in two places: Byline author: Author name included in the article byline. Non-byline author: Author name not included in the article byline but listed elsewhere, typically in an acknowledgment or article Information section.

- **Group author:** A group of individuals, usually involving multicentre study investigators, members of working groups, and official or self-appointed expert boards, panels, or committees, who wish to display a group name to indicate authorship.

- **Collaborator:** Another type of contributor who is a non-author member of a formal group and who contributes significantly to the work but does not qualify for authorship. These individuals may be listed as collaborators in an Acknowledgment or Article Information section.
- **Other contributors:** Anyone else who contributed in some meaningful way and who is not an author or a non-author collaborator. These individuals can be listed under Additional Contributions in an Acknowledgment or Article Information section.

### Reference

1. Fontanarosa P, Bauchner H, Flanagin A. Authorship and team science. *JAMA*. 2017;318:2433–7.



## EQUATOR Oncology: Enhancing the quality and transparency of health research

The EQUATOR Network regularly updates a website with resources for authors and editors.<sup>1</sup> It contains a compilation of documents to help medical writers to write research papers using reporting guidelines. As of January 2018, there are 389 reporting guidelines and a collection of comprehensive resources developed per specialty. The first specialist-collection, “EQUATOR Oncology”, compiles the information that are helpful to oncology researchers. The development of this cancer-specific project within the EQUATOR Network is funded by Cancer Research UK.

The first *EQUATOR Oncology Current Awareness Bulletin*, with a roundup of links to interesting publications and resources, was published in September 2017. The EQUATOR Oncology website has sections on the quality of reporting of randomised controlled trials in oncology; statistical controversies in clinical research; resources and references for oncology researchers; and a list of oncology-related organisations. Each section lists documents with the links to the original source. The series of 20 articles published in *Annals of Oncology* under the heading of “Statistical controversies in clinical research”, is a major asset for oncology researchers. It comprises four articles published



in 2015, six articles published in 2016, and 10 articles published in 2017. Most of these articles concern the poor quality of reporting research and the “beautification” practices of authors.

### Reference

1. EQUATOR Network, <http://www.equator-network.org/>.

## Researchers from wealthy nations contribute to illegitimate predatory journals

Two papers from the Ottawa-based research team Centre for Journalology (<http://www.ohri.ca/journalology/>) led by David Moher, are alarming the research community regarding a waste of human, animal, and funding resources.<sup>1,2</sup> Both articles relate to the matter of predatory journals, a global and growing problem contaminating all domains of science.

Although there is no universally accepted definition of predatory journals, the authors summed up criteria to identify them as those that

*... lack scientific rigour, with a poor or non-existent peer-review process and little or no editorial oversight to facilitate rapid publication, thus ensuring receipt of their Article Processing Charge (APC) from authors. Predatory journals are usually not indexed in established bibliometric databases although they often claim legitimate indexing. They also do not indicate how*

*their content will be archived in perpetuity — a key feature of standard online-only journals. They often have journal titles that mimic well-known authentic journals to confuse prospective authors. The APC for many of these journals is a magnitude cheaper than for legitimate open access journals.*

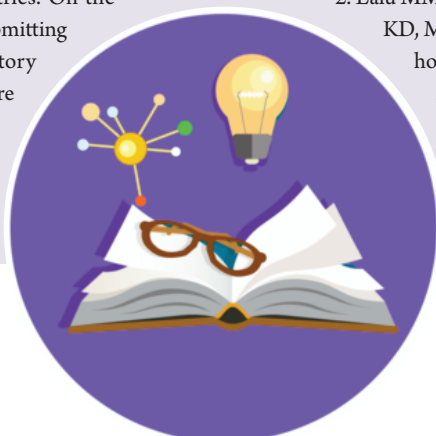
An analysis of 1,907 biomedical articles in predatory journals showed that among the top 10 countries to which the contributing authors belong were the United States, the United Kingdom, Japan, and China. In the past, we used to think that predatory journals concerned low and middle income countries. On the contrary, some authors submitting papers to these predatory journals know what they are doing. It is a way to enhance their curriculum vitae, to respond to the pressure to publish, and

to please institutional administrators who do not take measures to stop this waste.

Predatory journals are a global and growing problem contaminating all domains of science. A coordinated response by all stakeholders (researchers, institutions, funders, regulators and patients) will be needed to stop the influence of these illegitimate journals.

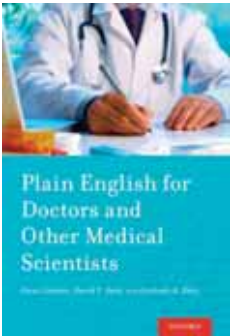
### References

1. Moher D, Shamseer L, Cobey K, Lalu MM, Galipeau J, Avey MT, et al. Stop this waste of people, animals and money. *Nature*. 2017;549:23–5.
2. Lalu MM, Shamseer L, Cobey KD, Moher D. How stakeholders can respond to the rise of predatory journals. *Nat Hum Behav*. 2017;1:852–5.





# In the Bookstores



## Plain English for Doctors and Other Medical Scientists

By Oscar Linares, David T. Daly, and Gertrude A. Daly  
Oxford University Press, 2017  
ISBN 978-0-19-065484-9 (paperback)  
£29.99. 232 pages.

In an ideal world, the deluge of information that comes our way from the tax office, insurance companies, lawyers, computer software companies, and suchlike would be written in plain English. Sadly, the reader is often left with the impression either that the author does not want us to understand the text, or that the author does not understand the concepts and, therefore, cannot explain them to anyone else. The main reason for using plain English in medical writing is so that any reasonable person can understand our written language and gather from it the messages we intend to convey.

The authors of *Plain English for Doctors and Other Medical Scientists* are a diverse team comprising a medical doctor who is not a native English speaker, a lawyer, and an English graduate. Thus they bring an educated and broad perspective to the subject. They tell us that, “Respecting a colleague’s time, by writing as clearly and as concisely as possible, is always the most professional way to write.” According to the authors, the target audience for this book is doctors who are not native English speakers but who read and write journal articles in English. However, the principles of writing in plain English may be applied widely, including to regulatory submission documents and writing for the public.

This is a self-study book that makes a worthwhile attempt to create a set of rules for writing in plain English. The authors have taken examples of written text from published journals, analysed the sentence structure, grouped their findings, and provided suggestions on how to make improvements.

The book is structured around three concepts: ease of reading, vivid language, and flow of logic. Each concept is subdivided into chapters that include related tips. The authors give instructions on how to

This is a worthwhile book for anyone who would like to take a structured approach to improving their plain English writing skills.

apply each tip and provide exercises to enable the reader to practise applying them. The book is more than an attempt to teach writing in plain English; it is a guide on how to write scientific English well.

The first concept in the book is “Take Charge of Your Reading Ease Score”. Here the authors introduce us to WSEG scores, which are a composite of the number of words (W), average sentence length (S), Flesch Reading Ease score (E), and Flesch-Kincaid Grade Level (G). The authors use WSEG scores to track changes in reading ease throughout the book. Not surprisingly, therefore, the chapters in the first concept focus on reducing sentence and word length and omitting any needless words.

The second concept, “Use Vivid Language”, includes some familiar suggestions such as using the active voice and avoiding nominalisation. However, there are also new ideas and constructive suggestions for bringing the language of medicine into the real world. The third concept, “Present Logical Reasoning Clearly,” provides some useful tips for organising the narrative to provide a clear and logical pathway for the reader.

Examples of each concept are given, but once the concept has been introduced the reader is then presented with a set of exercises without further assistance. It is not always clear what you are supposed to do. The suggested solution to each exercise is in a lengthy appendix, so the reader has to find the solution, then see how it has been applied to the exercise. There are also a lot of exercises, with the result that about a third of the book comprises suggested revisions.

Although practical exercises are worthwhile, with such a large proportion of the book dedicated to this type of learning, more guidance from the authors or worked examples could have been provided. In my opinion, at a minimum it would have been

**SECTION EDITORS**

 **Alison McIntosh**  
alison.mcintosh@iconplc.com

 **Stephen Gilliver**  
stephen.gilliver@gmail.com

more helpful if the authors had provided a solution to the first exercise for each tip before presenting the student with the full set of exercises.

Non-native English speakers should bear in mind that the authors of the book are American and some of the tips do not translate well into British English. For example, the authors suggest that the word *that* is unnecessary in the sentence, “The test confirmed that Natalia was pregnant.” As a native speaker of British English, I disagree.

I should also like to add a health warning about the humour. The authors introduce the term *medicus incomprehensibilis* to indicate impenetrable medical language. It is funny the first time you read it, but is overused.

The main criticism that I have of this book is that all of the conclusions are based on readability scores, rather than on readability testing. There is some impressive statistical analysis supporting the conclusion that the text has been improved, but no evidence that it was clearer or more easily understood by readers.

In conclusion, this is a worthwhile book for anyone who would like to take a structured approach to improving their plain English writing skills. However, it should be considered as a collection of good ideas rather than as a set of rules. Indeed, the authors themselves tell us to use our judgement. It is important to remember that language is living and fluid.

Reviewed by  
**Wendy Kingdom**  
Freelance, Wendy Kingdom Limited  
info@wendykingdom.com

# The Webscout

SECTION EDITOR



Karin Eichele

info@mediwiz.de

## Vaccines and immunotherapies

The first practice of immunisation in western countries dates back as far as 1796 when Eduard Jenner used cowpox to vaccinate a young boy against smallpox. This was soon followed by the first smallpox vaccine in 1798.

### History of vaccines

An impressive summary of history of vaccines and infectious diseases can be found at <http://www.historyofvaccines.org/>, one of the few websites that have been certified by the World Health Organization. This well-organised website also includes information about how vaccines work and how they are developed and manufactured, plus an animated activity tool.

### CDC website

The Centers for Disease Control and Prevention (CDC) is the leading public health institute in the US, and valuable information about current vaccines. The CDC also provides a frequently updated summary of the annual morbidity of vaccine-preventable diseases. The most recent can be found at <https://www.cdc.gov/vaccines/ed/surv/downloads/VPD-morbidity-slide1-mmwr-508.pdf>. Detailed information about the benefits and risks of vaccines are provided in Vaccine Information Statements, which can be found at <http://www.cdc.gov/vaccines/hcp/vis/current-vis.html>.

### WHO website

The WHO provides the most comprehensive summary of information required for assuring vaccine quality and safety (<http://www.who.int/immunization/en>). This includes current guidelines, international consensus on safety and quality issues, and technical advice to national regulatory authorities.

### Vaccine Adverse Event Reporting System

Because vaccines are intended for preventing disease in healthy people, comprehensive safety studies, intensive review of spontaneously occurring cases, and large epidemiological studies are needed. The Vaccine Adverse Event Reporting System, co-managed by the CDC and the FDA and available as an online tool at <https://vaers.hhs.gov/data.html>, collects post-marketing surveillance data on adverse events.



Currently, the system receives around 30,000 reports each year. The website also includes current and archived flu updates for healthcare professionals.

### ECDC website

The European Centre for Disease Prevention and Control (ECDC) (<http://ecdc.europa.eu/en>) was established after the outbreak of SARS in 2003 to strengthen Europe's defences against infectious diseases.

### EMA website

The regulatory framework for producing and using vaccines in the EU is provided by the EMA. Their website is at <http://www.ema.europa.eu/>.

### Open access article on the history of immunotherapy

Immunotherapies harness the body's own immune system to target and attack a disease. William Coley first attempted to harness the immune system for treating cancer in the late 19th century. In 1891, he injected a mixture of live and inactivated bacteria into patients' tumours and achieved complete remission of several types of malignancies. Cancer treatment

is currently a main focus of immunotherapy research. An informative timeline, with key events in the development of currently marketed immunotherapies is available in an open access article by Morrissey and colleagues at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5351311/>. The article explains that immunotherapies can be divided into two main types: "active", where the immunotherapy engages the host's immune response, and "passive", where the therapeutic agent directly neutralises the target and does not induce an immune response.

### YouTube video on anti-cancer immunotherapy by checkpoint inhibition

In 2013, the editors of *Science* chose active immunotherapies as the breakthrough of the year. In a video produced by the *Wall Street Journal*, available at <http://www.youtube.com/watch?v=ySG2AwpSZmw>, Dr James Allison, explains how CTL-4 blockade, also known as checkpoint inhibition, can enhance anti-tumour immunity and be used to fight against cancer. A text version is available at <http://crl.berkeley.edu/discoveries/the-story-of-yervoy-ipilimumab/>.

#### US NCI website on cancer vaccines

As described in a factsheet on the NCI website (<http://www.cancer.gov/about-cancer/causes-prevention/vaccines-fact-sheet>), cancer vaccines can be further subdivided in preventive and therapeutic types. Preventive vaccines are given to healthy individuals to keep certain cancers from developing, whereas therapeutic vaccines are given to cancer patients to reduce their existing tumours by boosting the immune system.

#### Cancer Research UK immunotherapy website

Cancer Research UK has a unique searchable database of all clinical trials in the UK. Their website also includes detailed information on “What is immunotherapy?” and “Types of cancer immunotherapy” at <http://about-cancer.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy>.

#### Marketing authorisation of cancer immunotherapies

In the EU, marketing authorisation for cancer immunotherapies follow the centralised procedure, which is described at [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000109.jsp&mid=WC0b01ac0580028a47](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47).

#### Cancer Drug Development Forum

There are many challenges to attaining approval and bringing cancer immunotherapies into clinical practice. The Cancer Drug Development Forum (<http://cddf.org/>) is a platform for experts from academia, oncologists, policy makers, representatives from health-technology-assessment bodies, the pharmaceutical industry, regulatory bodies, and patient organisations that works together with the EMA to aid in developing cancer drugs, including immunotherapies.

#### National Comprehensive Cancer Network

For the US market, the National Comprehensive Cancer Network ([www.nccn.org/professionals/physician\\_gls/default.aspx](http://www.nccn.org/professionals/physician_gls/default.aspx)) is a useful source for information on immunotherapy cancer treatment, including all kinds of guidelines.

#### Cancer.net

Cancer.net provides information from the American Society of Clinical Oncology, with support from the Conquer Cancer Foundation, to people living with cancer and those who care for and about them to help patients and families make informed health care decisions. The cancer.net website ([www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines](http://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines)) explains how cancer vaccines and immunotherapies work and provides links to clinical trials and details about reported side effects.

#### CNN podcast on cancer immunotherapies

In a recent podcast (<http://edition.cnn.com/2017/06/02/health/immunotherapy-cancer-debate-explainer/index.html>), CNN reports that there is “hope and hype” around cancer immunotherapies. They explain that immunotherapies are becoming a critical component of cancer care, especially in combination with standard treatments, and that they will be the main focus for cancer treatment over the next 5 years.

*Did you like this Webscout article? Do you have any questions or suggestions? Please feel free to get in touch and share your thoughts.*

**Angelika Schedel**  
[angelika-schedel@t-online.de](mailto:angelika-schedel@t-online.de)



# Lingua Franca and Beyond

“What is written without effort is, in general, read without pleasure”.

This statement,<sup>1</sup> attributed to Dr Samuel Johnson (1709–1784), a British author, linguist, and lexicographer, perfectly introduces the article by Julia Bates, who shares her thoughts on how to make our scientific writing easier to read. Julia’s advice is based on a simple rule of three C’s: Be clear, be concise, and be correct, which are easily written down but much more difficult to implement. To write clearly, concisely and correctly requires a lot of effort, thinking, and re-writing, but, as we can see in Julia’s article,

it definitely produces a lot of pleasure during the reading.

Just to follow the second c (be concise), I am stopping here, and wish you a lot of pleasure while reading Julia’s helpful hints.

## Reference

Samual Johnson. Wikiquote website. [cited 2017 December 18].

Available at: [https://simple.wikiquote.org/wiki/Samuel\\_Johnson](https://simple.wikiquote.org/wiki/Samuel_Johnson).

Maria Koltowska- Haggström

## SECTION EDITORS



Maria Koltowska-Haggström

maria.koltowska-haggstrom@propermedicalwriting.com

colleague or friend to read your draft, and then ask them what they thought were the main points of your paper. This will tell you whether your writing is clear.

Indeed, as Nancy Baron states in her book *Escape from the Ivory Tower: A Guide to Making Your Science Matter*:<sup>3</sup>

*No matter what your specialty, the keys to success are clear thinking, knowing what you want to say, understanding your audience, and using everyday language to get your main points across.*

I also suggest trying to follow the three C’s of effective paragraphs: context, content, and conclusion. In particular, the first sentence of a paragraph should state the single idea you wish to discuss (i.e., the topic or *context*). The topic sentence is then followed by the *content*, which provides more details to support the main idea. The final sentence of the paragraph provides the *conclusion* or purpose of the content, and may also help lead the reader into the next paragraph or idea.

## 2. Be concise

*So the writer who breeds more words than he needs is making a chore for the reader who reads.* – Dr Seuss

Try to stick to the point. Figure out what your main message is and stick to that topic. Remember that you don’t need to tell the reader everything you know about an entire field in one paper. You may have spent years learning about a particular protein or scientific technique, but it might not be relevant to the topic at hand. Ask yourself whether that sentence or paragraph helps the reader to interpret the findings presented in this particular paper. Also, check that you haven’t duplicated sentences or entire paragraphs in your introduction and discussion.

Another mistake is to use very long sentences, which can leave the reader confused and having to re-read the sentence multiple times. These lengthy sentences can be spotted easily if you read your paper aloud. If possible, try to break

## How to make your scientific paper easier to read

Do you ever wonder how many people are actually going to read your paper? I mean, not even my mother has read my papers, and with good reason:

*There is no form of prose more difficult to understand and more tedious to read than the average scientific paper.* – Francis Crick<sup>1</sup>

It is not surprising that scientific papers are difficult to understand; they are usually written for a very specific audience, typically fellow scientists within a niche field. This means that the article is often full of technical information and jargon.

But wouldn’t it be nice if your paper was read by scientists *outside* your field? Or by medical professionals who may implement some of your findings in their treatment plans? Or by journalists who could inform the wider public of the exciting work that you are doing?

Communicating your work clearly to those outside your field is especially important for any research involving vaccines and immunotherapies. Misinformation about vaccines and misleading reports concerning adverse events in the media can have devastating consequences, such as the recent measles outbreaks in Europe resulting from decreasing vaccination rates.<sup>2</sup>

Therefore, we all have a responsibility to communicate scientific research in such a way that it is understood by a broad audience. Your goal should be to inform others, not impress your peers.

The key to making scientific papers easier to read is to follow the three C’s of good writing, namely, to be clear, concise, and correct.

## How do the three C’s apply to science writing?

### 1. Be clear

*My aim is to put down on paper what I see and what I feel in the best and simplest way.*

– Ernest Hemingway

Just like Hemingway, you should write your paper in the simplest way. Try not to over-complicate things, the science is usually complicated enough. When possible, use words that are familiar to the reader; for example, “burgeoning” becomes “increasing” and “aetiology” becomes “cause”. Do not try to impress your reader with complicated phrases or words.

Define or explain any terms that may not be known to the reader. As a general rule, try to make sure that your text is understandable to an undergraduate-educated scientist outside their field of specialty.

Another good tip is to get a

Therefore, we all have a responsibility to communicate scientific research in such a way that it is understood by a broad audience.



them down into shorter sentences to improve the readability.

You should also remove unnecessary words. For example: “is a reflection of” becomes “reflects”; “we performed a detailed analysis of” becomes “we analysed”; “the question as to whether” becomes “whether”; “in order to” becomes “to”; and “a large majority” becomes “most”. Cutting out these words will also help improve the overall readability.

Another tip for making your paper more concise is to use your references wisely. Instead of providing all the detailed background to a topic, simply pick out the most relevant points to your paper, and then direct the reader to a more comprehensive review article if they wish to learn more.

### 3. Be correct

The third **C** refers to both correct grammar and correct content. The correct use of punctuation and grammar will improve the readability of your paper. Consider the following sentence:

*Inclusion criteria for the study were aged between 10 to 15 years intravenous administration of antibiotics diagnosed with sepsis and no respiratory complications.*

This sentence makes no sense. But with the correct punctuation, it becomes much easier to read:

*Inclusion criteria for the study were: (i) aged between 10 to 15 years; (ii) intravenous administration of antibiotics; (iii) diagnosed*

**Being concise at the expense of being correct is not acceptable when reporting a scientific method or its results.**

*with sepsis; and (iv) no respiratory complications.*

The content (i.e., the science) also has to be correct. Be specific. For example, “We analysed 115 patients with non-small cell lung cancer treated with single-agent nivolumab” is not the same as “We analysed 115 cancer patients treated with immunotherapy”. Being *concise* at the expense of being *correct* is not acceptable when reporting a scientific method or its results.

## Conclusion

We all have a responsibility to communicate scientific research clearly and correctly. This may help us to overcome the increasing problems in science communication, whereby scientific evidence fails to resolve public dispute over the risks and benefits of discoveries such as childhood vaccines.<sup>4</sup>

So, the next time you sit down to write a paper, remember the simple three C’s of good writing. Writing clearly, concisely, and correctly does take time, but by following these simple tips, your paper should reach a much broader audience.

## Additional resources

The *Nature* website has a great article on writing scientific papers in its section on *English Communication for Scientists*. Available from: <https://www.nature.com/scitable/ebooks/english-communication-for-scientists-14053993/writing-scientific-papers-14239285>.

Richard Threlfall wrote a series of articles on the Chemistry Views website. He takes you through each section of your paper and gives practical tips on how to improve it. There is also a free webinar: How to Write High-impact Research Papers. Available from: [http://www.chemistryviews.org/details/education/5202161/Tips\\_for\\_Writing\\_Better\\_Science\\_Papers.html](http://www.chemistryviews.org/details/education/5202161/Tips_for_Writing_Better_Science_Papers.html).

For basic grammar queries, check out sites like Grammar Girl: <http://www.quickanddirtytips.com/education/grammar>.

## References

1. Crick F. The astonishing hypothesis: the scientific search for the soul. Touchstone, USA; 1995. ISBN: 0684801582.
2. World Health Organization. Communicating science-based messages on vaccines. B World Health Organ. 2017;95:670–1. doi: 10.2471/BLT.17.021017.
3. Baron N. Escape from the ivory tower: a guide to making your science matter. Island Press; 2010. ISBN: 9781597269650.
4. Kahan D. A risky science communication environment for vaccines. *Science*. 2013;342(6154):53–4. doi: 10.1126/science.1245724.

**Julia Bates**  
**Science Write**  
[www.sciencewrite.com.au](http://www.sciencewrite.com.au)

Note: This article has been adapted from a blog post by Julia Bates originally published at

# Teaching Medical Writing

## Learning to write a good story: Academic writing for qualitative health researchers

Since 2014, I have offered a four-day course on academic writing for qualitative health researchers at the University of Southern Denmark. I tell the participants, mostly PhD students with backgrounds in the health professions, that “learning to write a good story” is the central aim of the course. But why is a good story important? What makes a good story? And how can one learn to write one? In this article, I explore these questions in the context of teaching academic writing to qualitative health researchers.

### The importance of a good story

Qualitative research is gradually being accepted in the medical and health sciences as a valid mode of knowledge production, and a variety of medical journals are willing to publish findings derived from it. In these contexts, qualitative research is often part of a mixed methods approach that prioritises quantitative methods, e.g., a randomised controlled trial complemented by a nested qualitative study with a small number of in-depth interviews or focus group discussions. Qualitative health research also of course stands alone, reflecting the broad range of academic disciplines that draw on qualitative research, including medicine, nursing and the health sciences, medical anthropology, sociology, philosophy and geography.

The strength of qualitative research methodologies lies in their ability to bring to the foreground the diverse perspectives of the many players involved in healthcare – patients, relatives, health professionals of all kinds, policy makers, etc – and their multifaceted relationships and practices. These perspectives are critical in developing a deeper understanding of everyday life with illness, and they add important dimensions of knowledge and evidence to improving care, services and policy.<sup>1</sup> Compared with quantitative research, however, qualitative health research tends to be undervalued, and hence underused, in medical and health sciences. A good story with a compelling argument can contribute towards shifting the balance.

### Building blocks of a good story

Wolcott emphasises that, especially for qualitative researchers, “writing well is neither a luxury nor an option ...; it is absolutely essential”.<sup>2</sup>

However, as Sandelowski<sup>3</sup> notes,

*...qualitative researchers may offend with turgid prose, seemingly endless lists of unlinked codes and categories, dangling participles, and dizzying arrays of multiply hyphenated and, sometimes, nonexistent words that convey nothing more than the writer's willingness (albeit unintended) to destroy the English language (p375).*

This is harsh criticism, particularly for researchers writing in their second or third language, as many authors do when publishing in international peer-reviewed journals.

Sandelowski also points to two early main challenges facing qualitative researchers when writing up their research.<sup>3</sup> First, writers must decide how to tell their story by identifying the style most suitable to the research, purpose, and audience. Unlike the IMRAD (Introduction, Methods, Results, and Discussion) format that dominates in medicine and the health sciences, one size does not fit all in qualitative research writing.<sup>3</sup> Second, researchers must choose which story, of the many possible stories based on their data set, to tell. That is, they must determine a story's central point or story line,<sup>3</sup> and the argument they wish to make. They have to move from retelling participants' stories through summarising the data, to transforming the data through analysis and interpretation. As Coffey and Atkinson note, “Data are there to think with and about”; but “the generation of ideas can never be dependent on data alone” (p153).<sup>4</sup> Instead, through the selective use of data, writers exemplify and illustrate the story they aim to tell.<sup>4</sup> A “good story” includes the formulation of an argument that runs like a red thread through the text, while also holding it together. This requires writers to “construct a well-designed story that involves the reader along the way and results in a compelling message” (p115).<sup>5</sup>

Many of the participants I teach are not aware of the crucial difference (and tension) between writing as a form of thinking<sup>2</sup> or a method of inquiry<sup>6</sup> – where we *reflect* on our research and data – and the writing up of the final product as a peer-reviewed article, monograph, or book chapter – where we move beyond our data to *present* what our research and data mean.<sup>2,4</sup> For

### SECTION EDITOR



Claire Gudex

Claire.Gudex@rsyd.dk

this reason, I use the writing process and its many associated phases and activities as the overall structuring device for teaching the writing of a good story.

### Learning to write a good story

The course material comprises selected reading for each day, together with a real-life writing example based on one of my articles.<sup>7</sup> This example illustrates the entire writing process from the early inception of a paper to its publication, and includes: i) a short conference paper and associated PowerPoint presentation, and the conference Call for Papers; ii) the developed manuscript submitted to a journal and the reviewers' comments; iii) the first and second revisions together with my responses to the reviewers; and iv) the final published paper.

The course format is interactive and discussion-based. It combines short lectures that introduce key points about academic writing and the reporting of qualitative research with discussions and individual and group exercises that form an integral part of learning how to report qualitative research. Throughout the course, different strategies for *writing* and *writing up* are practised, including those that can be useful in overcoming procrastination and writer's block. The real-life writing example is used extensively during the 4 days; for example, to analyse how the manuscript title evolved over time; to explore the development and presentation of the argument; to see how paragraphs are constructed; and to learn how reviewer feedback can be integrated into the manuscript. Some class exercises and the homework assignments focus on the participants' own manuscripts, thus enabling participants to improve their own work in a supportive environment.

The 4-day course is run over 4 weeks, with one 5-hour day (including breaks) each week. On Day 1 the writing process is introduced: We examine the characteristics of academic writing in general and in different academic disciplines; we also begin to explore the characteristics and

demands of reporting qualitative research for different audiences and start to discuss the selection of a suitable journal.

Day 2 focuses on the structure of the manuscript: how to write abstracts for different disciplines, journals, and purposes; how to configure arguments; and how to draft an article outline, or what Wolcott refers to as “The Plan”.<sup>2</sup> Participants also practice writing about a theoretical concept or analytical perspective.

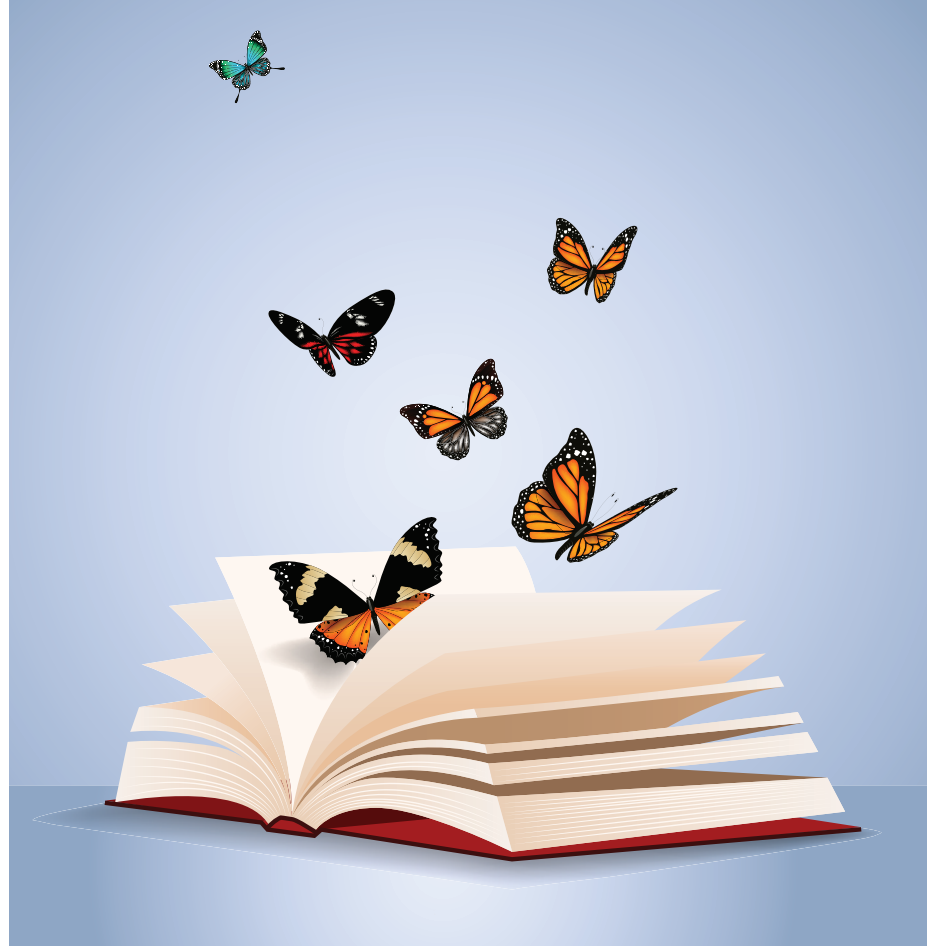
Day 3 shifts the focus to the various text elements and how to revise a draft. We discuss how to build strong paragraphs, use quotations (from other authors and from research participants’ stories), and include signposts throughout an article. Strategies for avoiding “plagiarism by mistake”<sup>8</sup> and for extending vocabulary are also tried out. Participants who are writing up qualitative research in their second or third language find this particularly important, as they often struggle with limited vocabulary and a resulting sense of flat writing.

Day 4 starts with text revision, moving to how to edit and polish drafts. We then discuss the article submission process: the do’s and don’ts when submitting an article; how to survive the review process and use reviewer feedback constructively; responding to reviewers’ comments; and how to resubmit (or search for another journal). A discussion on what it means to be an (academic) writer concludes the day.

By the end of the course, we have explored key stages in the writing process, analysed texts of various lengths and purposes, and discussed and practised a variety of writing strategies and writing tasks. Most participants value the opportunity to make progress on their own text while also stepping back from their own writing and to engage with the development of a real-life manuscript from inception to publication.

## Concluding remarks

Good stories come in many forms, but they all have a central story line and aim to engage the reader. Although my background is in anthropology, my aim is to demystify the writing process and the writing up of qualitative research without limiting it to a particular disciplinary field or writing style. This includes acknowledging that writing can be learnt and offering strategies for when the going gets rough, as it so often does for PhD students – especially for non-traditional students and those not



writing in their mother tongue.<sup>9</sup> Teaching academic writing also entails the acute awareness that “writing is not an innocent practice”; rather, “the technologies of writing create gendered social texts where desire, intimacy, power, class, race, ethnicity, and identity come alive” (p568).<sup>10</sup> This combination makes teaching academic writing for qualitative health researchers both stimulating and satisfying. Moreover, the participants appreciate the chance to critically reflect on their writing in sympathetic surroundings, given the unrelenting pressures to publish or perish.

## References

1. Barry CA. The role of evidence in alternative medicine: contrasting biomedical and anthropological approaches. *Soc Sci Med.* 2006;62(11):2646–57
2. Wolcott HF. *Writing up qualitative research.* Newbury Park, Calif.: Sage; 1990.
3. Sandelowski M. Writing a good read: strategies for re-presenting qualitative data. *Res Nurs Health.* 1998;21:375–82.
4. Coffey A, Atkinson P. *Making sense of qualitative data: complementary research strategies.* Thousand Oaks, Calif.: SAGE Publications; 1996.
5. Alvermann DE, O’Brien DG, Dillon DR. On writing qualitative research. *Read Res Q.* 1996;31(1):114–20.
6. Richardson L. Writing: a method of inquiry. In NK Denzin, YS Lincoln (eds.) *Handbook of Qualitative Research.* 2nd ed., pp. 923–948. Thousand Oaks, Calif.: Sage Publications; 2002.
7. Nissen N. Naturalness as an ethical stance: idea(1)s and practices of care in western herbal medicine in the UK. *Anthropol Med.* 2015;22(2):162–76.
8. Mewburn I. How to plagiarise (by mistake). 2013. Available from: [https://prezi.com/yms9arr\\_ubt8/how-to-plagiarise-by-mistake/](https://prezi.com/yms9arr_ubt8/how-to-plagiarise-by-mistake/).
9. Nissen N. Strange encounters: reflections on authoring a doctoral thesis. 2011. Available from: <https://www.dur.ac.uk/writingcrossboundaries/postgraduateonwriting/ninanissen/>.
10. Denzin, NK. Two-stepping in the ’90s. *Qual Inq.* 1999;5(4):568–72.

The strength of qualitative research methodologies lies in their ability to bring to the foreground the diverse perspectives of the many players involved in healthcare – patients, relatives, health professionals of all kinds, policy makers, etc – and their multifaceted relationships and practices.

**Nina Nissen**  
Department of Public Health  
University of Southern Denmark  
Odense, Denmark  
[ninissen@health.sdu.dk](mailto:ninissen@health.sdu.dk)



EMWA

EUROPEAN  
MEDICAL  
WRITERS  
ASSOCIATION

## 6th EMWA Symposium – Thursday, May 3, 2018 at the Spring EMWA conference in Barcelona, Spain

### Medical Devices and Technologies – Emerging Opportunities for Medical Communicators

The 6th EMWA symposium day will focus on medical devices in general, the recent changes in the European legislation, and opportunities for medical writers. The symposium is for regulatory writers and medical communicators alike and will provide the perspectives of different stakeholders, including legislators, notified bodies, medical device companies, patient representatives, and reimbursement professionals.

The preliminary symposium programme is:

- Introduction to medical devices
- Transferrable skills: from drugs to medical devices
- The new Medical Device Regulation (MDR) and its implications for medical writers
- MDR and MEDDEV: What notified bodies are looking for in Clinical Evaluation Reports (CERs)
- Patient user, apps, technologies, security, and potential failures
- Databases and tools: systematic reviews
- From bench to publication: All you need to know about medical devices based on a case example
- Publication planning during device life cycle
- European medical devices reimbursement strategies and associated documents

We look forward to welcoming you to our EMWA Symposium.



# Good Writing Practice

## Inter-sentence discontinuity 2

Misplacement discontinuity and omission: Continuity markers



### Introduction

This is the second of two articles on inter-sentence discontinuity. In this article, we consider the following examples of misplacement: Part 1, Results and Conclusion in the Introduction section; Part 2, Justification for Hypothesis and Hypothesis in the Materials and Methods section. Both are counter to the expectations of a reader in the profession who expects anticipated conceptual components to be in appropriate sections of a journal article, not because of rules but because of discontinuity to a developing argument.

Paragraph lengthiness and complexity without discernible continuity can be minimised by a forecast and a backtrack marker of the information pattern. Omission of forecast continuity markers (subheading, end-of-sentence;

Part 3) and backtrack continuity markers (determiners: definite article, indefinite pronoun, demonstrative adjective; Part 4) impede immediate comprehension.

### Part 1 – Results and conclusion in the Introduction section

#### Example: Introduction section

*Bacteriorhodopsin (bR), a photochromic protein in the purple membrane of the archaebacterium Halobacterium salinarium, is excited to a metastable state as light is absorbed, a metastable state that is characterised by a refractive index greater than that of the unexcited state. The dependence of the refractive index of bR on incident light intensity was reported for only relatively low intensities, substantially lower than*

### SECTION EDITORS



**Wendy Kingdom**

info@wendykingdom.com



**Amy Whereat**

amy.whereat@speaktthespeech.fr

*the maximum laser intensities available. Consequently, we tested (by using a Z-scan technique) the behaviour of bR in response to high intensities. The results were that the refractive index is positive in response to low incident intensities, but the change becomes zero and then negative beyond a threshold intensity.*

*In conclusion, the results indicated the limitations of the previously accepted model for bR and provide a new model for greater potential uses (e.g., self-limiting filters, high-speed shutters).*

In this example, the first sentence describes the pertinent background to the research problem, the second sentence describes the research problem, and the third sentence describes the objective. However, the remainder of the text (underlined) can be categorised as results and conclusion-consequence.

### Revision

*Bacteriorhodopsin (bR), a photochromic protein in the purple membrane of the archaebacterium Halobacterium salinarium, is excited to a metastable state as light is absorbed, a metastable state that is characterised by a refractive index greater than that of the unexcited state. The dependence of the refractive index of bR on incident light intensity was reported for only relatively low intensities, substantially lower than the maximum laser intensities available.*

*Consequently, we tested (by using a Z-scan technique) the behaviour of bR in response to high intensities.*

### Notes

Placement of results and conclusion in the Introduction section is an over-statement because these components would be stated in the

abstract and, of course, in the results and discussion section. Inclusion of results and conclusion in the Introduction section seems not only redundant to the Abstract (and “pre-dundant” to the Results and Discussion sections) but also, by such repetition, an overstatement. However, conceptual component misplacement is a less severe distraction than conceptual component omission because misplacement is a lack of organisation not an omission of essential information. (In both the example and the revision, the justification for the hypothesis and the hypothesis are missing between the research problem and the objective.)

Misplacement can be considered as the other side of omission; that is, placement of a conceptual component into an inappropriate section may result in an omission of the component in an appropriate section.

## Part 2 – Hypothesis justification and hypothesis in the Materials and Methods section

### **Example: Materials and Methods section**

It has become increasingly important to streamline occupational therapy intervention for patients who are experiencing shorter length of stays. The national average length of stay for a rehabilitation patient is between 10 and 12 days. Therefore, a family and/or caregiver education is paramount for safe discharge to the home setting. This study involved a convenience sample of 10 patients over a 6-week period in the acute rehabilitation unit of a hospital (IRB was obtained prior to initiating the study). The patients were a combination of men and women who had a variety of physical disabilities (e.g., CVA, TBI, SCI). Exclusion criteria were moderate-to-severe cognitive, auditory, and visual deficits.

In this example, the hypothesis justification and hypothesis are included in the Materials and Methods section, whereas this information should have been included in the Introduction.

### **Revision**

*This study involved a convenience sample of 10 patients over a 6-week period in the acute rehabilitation unit of a hospital (IRB was obtained prior to initiating the study). The patients were a combination of men and women*

*who had a variety of physical disabilities (e.g., CVA, TBI, SCI). Exclusion criteria were moderate-to-severe cognitive, auditory, and visual deficits.*

### **Notes**

There is no need to repeat in the Materials and Methods section conceptual components from the Introduction. Although it is not uncommon to forget that each section of the journal article is part of a continuum, readers of journal articles respond negatively to repetition between sections as an indication of author lack of discipline.

## Part 3 – Forecast markers

Here we look at two examples of discontinuity resulting from omission of a forecast marker.

### **Example 1 (Subheading): Materials and Methods section: method**

*At the Chilao study site (San Gabriel Mountains, California), after soil temperature measurement (LaMotte Chemical dial thermometer), small samples of soil (2 m intervals) were collected (trowel), placed into a bag, dried, and mixed. A few tablespoons of soil were dried (to the nearest ounce), heated (4 h, 550°C), reweighed (25°C), and the amount expressed as a percentage of total weight.*

*A LaMotte Deluxe TurfLab Soil Kit (Model TL-2) was used to determine the following: nitrate nitrogen (mixed acid reagent and nitrate reducing reagent); phosphorus (NF extracting solution and charcoal suspension); potassium (K solution); iron (iron reagent #1 and #2); calcium and magnesium (Schwarzenback EDTA titration method). Nitrate, phosphorus, and iron were measured colorimetrically.*

### **Revision**

*Collection and processing – At the Chilao study site ... [paragraph continues as above].*

*Chemical analyses - A LaMotte Deluxe Turf Lab Soil Kit ... [paragraph continues as above].*

### **Notes**

In the example, the omission of in-text subheadings renders the shift inexplicit from one research activity (collection and processing) to another (chemical analyses). Continuity between dense paragraphs consisting of different types of

information can be made explicit by use of subheadings.

### **Example 2 (end-of-sentence appositives): Introduction section: research problem pertinent background**

*To obtain the best performance from processors, two essential assistants can be considered. The compilers maximise the parallelisation and balance workloads. The interconnects among clusters are another requirement for improving the processor performance by overcoming the partitioning overhead as inter-cluster communications.*

### **Revision**

*To obtain the best performance from processors, two essential assistants can be considered: **compilers and interconnects among clusters.** The compilers maximise the parallelisation and balance workloads. The interconnects among clusters are another requirement for improving the processor performance by overcoming the partitioning overhead as inter-cluster communications.*

### **Notes**

Forecasting the assistants (compilers and interconnects among clusters) as appositives at the end of the first sentence provides explicit continuity to the second and third sentences.

## Part 4 – Backtrack markers

In addition to functioning grammatically as a marker of uniqueness, the definite article *the* denotes that a noun was previously mentioned and, thus, known to the reader and author. The definite article thus functions as a marker of continuity, intra- and especially inter-sentence. A continuity gap can occur if the definite article or a stronger type of determiner is missing. In this section, examples are arranged as a noun pre-mentioned in a contiguous sentence (Example 1); and a noun pre-mentioned in a previous section (Examples 2 and 3).

### **Example 1 (the and such in a contiguous sentence): Introduction section: research problem pertinent background**

*Bacteria can spread quickly from the cavities to the apical through the straight root canals of baby teeth, resulting in infected bone and periodontal tissue. Infection will impair craniofacial development.*

### Revision 1

Bacteria can spread quickly from the cavities to the apical through the straight root canals of baby teeth, resulting in infected bone and periodontal tissue. **The** infection will impair craniofacial development.

### Revision 2

Bacteria can spread quickly from the cavities to the apical through the straight root canals of baby teeth, resulting in infected bone and periodontal tissue. **Such** infection will impair craniofacial development.

### Notes

Some continuity is provided by echo of the word *infection*, which fills the continuity gap between the first and second sentence. In Revision 1, further continuity is provided by *the*. In Revision 2, the indefinite pronoun determiner *such* renders the continuity explicit. Usage of the determiner *this* would be a little less emphatic, and *the* would be even less so. Thus, there seems a hierarchy of determiner-elicited continuity emphasis: *such* > *this/that* > *the*.

The subject of a sentence is often preceded by

the definite article *the*, maybe because the subject position is the site for known information and the predicate site for new information.

### Example 2 (the for an antecedent in a previous section): Materials and Methods section

Three hepatoma cell lines were used in this experiment.

### Revision

**The** three hepatoma cell lines were used in this experiment.

### Notes

Without *the*, it would seem that *three hepatoma cell lines* is mentioned for the first time, forgoing not only *their prior mention but their importance in context*.

### Example 3 (many of the for antecedents in a previous section): Materials and Methods section: method

Many studies were performed in vitro.

### Revision

Many **of the** studies were performed in vitro.

### Notes

Without *of the*, there is no denotation that all of the studies were previously mentioned. *The* used alone as in *many the* is unconventional. Other determiners that require *of* are *none* and *some*. In contrast, *all the* sounds conventional, but *all of* would be consistent with all of the others.

### Summary

The misplacement of a conceptual component from one section to another will be viewed as redundant over-emphasis – not without value in a grant application, but distracting in a journal article.

Omission of forecast or backtrack markers decreases paragraph continuity, resulting in impeded immediate comprehension.

**Michael Lewis Schneir, PhD**  
Professor, Biomedical Science  
Ostrow School of Dentistry  
University of Southern California  
Los Angeles, CA, USA  
schneir@usc.edu



# Save the date

The 47th EMWA Conference in  
**Warsaw, Poland**  
November 8–10, 2018  
For more information:  
<https://www.org/conferences/future-conferences/>

# Medical Devices

## Editorial

Welcome to the world of medical devices! Increasing regulatory requirements lead to an increasing demand for medical writers. EMWA is acknowledging this emerging field in several ways:

- It is organising a medical device symposium at the next Spring conference in Barcelona, flanked by two medical device workshops.
- A medical device track/certificate is in preparation.
- A medical device special interest group has been founded.
- This section will become a regular contribution to MEW.

*Do you have anything particular you would like to see in this section? Or do you want to contribute to it? We would love to hear from you!*

Beatrix

## SECTION EDITOR



**Beatrix Doerr**

Beatrix.doerr@coriuvar.com

## EMWA's Medical Device Symposium "Medical Devices and Technologies Emerging Opportunities for Medical Communicators"

The 6th EMWA symposium day will focus on medical devices in general, the recent changes in the European legislations, and opportunities for medical writers. The symposium is for regulatory writers and medical communicators alike, and will provide the perspectives of different stakeholders, including legislators, notified bodies, medical device companies, patient representatives, and reimbursement professionals.

The preliminary programme is as follows:

### Introduction to the medical device world

**Claudia Frumento, ICiMT – International Communication in Medicine and Technology**

The field of medical devices is a broad one: wheelchairs, contact lenses, X-ray machines and implantable cardioverter defibrillators are all medical devices, but they have completely different uses and pose different risks to the patient, the user and the environment. Thus, medical devices are classified based on their risk profile, affecting the processes required for their market release. Medical writers play a key role in this process: they write some of the most important documents required for market approval such as the Clinical Evaluation Report, Clinical Investigational Plan, and Clinical Investigation Report. This introductory session gives an overview of the terminology used, the classification system, the regulatory pathways and the role of MW in preparing the documents required.

### Medical writing and transferable skills: From pharmaceuticals to medical devices

**Gillian Pritchard, Sylexis Ltd.**

The idea of writing about medical devices might seem daunting—after all, there are so many of them, ranging from the simplest wound dressing to the most sophisticated imaging equipment. However, typical “pharmaceutical” documents such as clinical study protocols, clinical overviews and summaries, and summaries of product characteristics have their equivalents for medical devices. Just as “pharmaceutical” writing is governed by guidelines and directives, the same is true for medical devices. Similar skills are needed for pharmaceutical and medical device writing, namely the ability to follow guidelines, use templates, evaluate medical literature, and write clearly and objectively. So a writer accustomed to writing about pharmaceuticals may discover that they can just as easily write about medical devices.

### The new Medical Device Regulation (MDR) and its implications for medical writers

**Paul Piscoi, Scientific Policy Officer, Unit Cosmetics and Medical Devices, European Commission**

In May 2017, two new regulations were published namely Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices, foreseen to enter into application 26 May 2020 and 26 May 2022 respectively. The presentation will start by outlining the key new features of these regulations with a focus on the clinical/performance aspects, which represent one of the

major overhauls of the legislative framework for medical devices. This section will be supplemented with an outline of implementation priorities as well as the transitional timelines and measures. An overview of the existing guidance will follow along with plans for its updating in order to bring it in line with the requirements of the new regulations. The core of the presentation will cover sections on the clinical/performance requirements relevant to medical writers along with the latest novelties brought about by the activities of the Clinical Investigation and Evaluation Working Group. This will include information regarding the development of guidance on the Summary of Safety and Clinical Performance, various templates, an addendum to MEDDEV 2.7/1 rev 4 and EUDAMED as the future database for medical devices. The importance of scientifically sound and well written clinical sections of the medical devices technical files and the role of medical writers will be covered at the end.

### MDR and MEDDEV; what notified bodies are looking for in clinical evaluation reports

**Ito Udofia, Head of Medical Device Notified Body, Underwriters Laboratories**

The clinical evaluation is an essential part of the technical documentation, which manufacturers require to document their compliance with the general safety and performance requirements. The new Medical Device Regulations places greater emphasis on the use of clinical data to demonstrate compliance with the general safety and performance requirements. With the increased scrutiny expected with the new

regulations, the guidance document, MEDDEV 2.7.1 (rev 4) was published in July 2016, to prepare manufacturers and notified bodies for the key requirements of clinical evaluation. Although compliance with Revision 4 of the MEDDEV does not mean compliance with the new regulations, it brings manufacturers closer to compliance. This presentation focuses on the key requirements and what notified bodies will be looking for when reviewing clinical evaluation reports. By understanding what the notified bodies are looking for, clinical evaluation reports can be better written and presented for assessment.

### Panel session:

#### Impact of new regulations

**Panel led by Jane Edwards, Head of Global Communications – Medical Devices, BSI Group**

**Panelists: Claudia Frumento, Gillian Pritchard, Paul Piscoi, Itoro Udofia, Raquel Billiones, Beatrix Doerr**

#### **Apps, technologies, security, potential failures** **Kyle J. Rose, International Diabetes Federation (IDF)**

Thousands of health apps are available today, often using different approaches for different audiences. They range from fitness/nutrition trackers to apps connected with existing medical devices, such as blood monitors and complex medication infusion systems. Using diabetes as an example across chronic disease, this talk will propose a framework to think about apps, potential classification categories, and important differences such as primary use cases, medical content/nature, as well as software development infrastructure. Also discussed will be: (a) the impact of apps on patients, health care professionals, and other healthcare stakeholders; (b) the potential role of apps in our health systems; and (c) current limitations and progress (including clinical evidence, data ownership and safety).

#### **Systematic reviews: Finding the right information for medical device clinical evaluations and post-market surveillance for biomedical searching**

**Ivan Krstic, Senior Product Development Manager at RELX Group, EMBASE/Elsevier**

Information found in the biomedical literature strengthens every stage of the medical device life cycle, from concept and design through clinical trials to commercial release and reimbursement, as well as post-market surveillance. Embase provides all the relevant information and essential evidence for creating high-quality systematic reviews that support medical device development and post-market surveillance. In this session, Senior Product Development Manager Embase Dr Ivan Krstic will discuss:

- European Medical Device Clinical Evaluation Report guidelines (MEDDEV 2.7/1)
- the importance of biomedical literature in preparing successful Clinical Evaluations and in remaining compliant with post-market surveillance requirements
- a case study on how to design effective literature searches for CER to identify:
  - device clinical performance
  - comparisons of device with existing device(s)
  - device safety – finding adverse device effects

#### **From bench to publication: All you need to know about medical devices based on a case example**

**Myriam Stieler, Director Medical Affairs, Biotronik**

This presentation will build on the previous ones and will show the complete life-cycle of a medical device based on the practical example of a novel scaffold technology. It includes possible pitfalls, setbacks, and considerations in data interpretation. The aim is to provide a robust overview of the device development that will facilitate understanding clinical data obtained from medical device studies.

#### **Generating the necessary clinical evidence through product life cycle communication strategy**

**Patrice Becker, Global Director Scientific Communications, Medical Affairs, Medtronic**

With the current changes in the medical device industry, with new regulations, and with a move from a traditional customer base of health care professionals to health care administrators, it is more important than ever to have peer-reviewed

clinical evidence and to tell a “story” of a medical device throughout its lifecycle. This session will discuss the variety of studies worthwhile to publish (from pre-clinical animal models to post-approval studies), the regulatory context of publications, how to create an evidence-based strategy throughout the lifecycle of the product, possible challenges, and an example of an effective publication strategy.

#### **European reimbursement strategies and associated documents**

**Oleg Borisenko, CEO MedTech Reimbursement Consulting**

Market access is extremely important for the success of innovative technologies. This includes obtaining reimbursement (ability to pay for procedure/device) and funding (willingness to pay). To establish reimbursement and funding, multiple activities might be needed, including application for procedure code and change of the Diagnosis-Related Group (DRG) system, applications for reimbursement review, and health technology assessment. In this presentation, one of the leading European market access experts, Oleg Borisenko, will outline some of the specifics of the market access processes and how medical writers can contribute to these processes. In particular, the following questions will be addressed:

- What are the typical reimbursement barriers for medical devices in Europe?
- What are the typical requirements to overcome reimbursement barriers?
- What can be a role for a medical writer to support reimbursement activities?
- What is the concept of the value dossier?

### Panel session:

#### Medical devices 10 years from now

**Panelists: Jane Edwards, Kyle J Rose, Myriam Stieler, Patrice Becker, Oleg Borisenko, Ivan Krstic**

**Raquel Billiones**  
rbilliones@clinipace.com  
**Beatrix Doerr**  
Beatrix.doerr@gmail.com



## Medical device workshops in Barcelona

The medical device symposium will be flanked by two medical device workshops held on May 2 and 4:

### Basics of writing for Medical Devices under the MEDDEV rev. 4 and new MDR

**Claudia Frumento, ICiMT – International Communication in Medicine and Technology**

The objective of this workshop is to provide an introduction to the field of medical devices and associated document requirements. Areas covered include: classification of medical devices; basic regulatory issues regarding the approval and marketing of medical devices; recent changes in regulatory requirements and how these impact the medical writer's role; and some of the most common medical communication documents.

A syringe, a knee prosthesis, a computerised tomography (CT) scanner, an external defibrillator, and a pacemaker are all medical devices, but they belong to different risk classes. The new regulations (MEDDEV 2.7/1 rev.4 and Medical Device Regulation) define a core documentation set required for regulatory compliance of these

devices. And this can be challenging for the industry and the Medical Writer.

Focusing on a set of different medical devices, the main elements of the workshop will introduce:

- what a medical device is and why and how devices are classified
- key documentation for regulatory compliance and market release of a medical device
- medical communication texts: particularities for medical devices

### Literature review for medical devices

**Gillian Pritchard, Sylexis Ltd.**

The aim of this workshop is to understand how to write a literature review as part of a Clinical Evaluation Report. Participants will learn how to prepare a literature review to current MEDDEV 2.7/1 rev. 4 requirements. The workshop will explain:

- the role of the literature review in the clinical evaluation of a medical device

- the scope of the literature review
- literature search strategies for the subject device and state of the art (current knowledge)
- how to write the state of the art section
- how to screen and appraise the literature
- data extraction
- the analysis and presentation of the literature in the CER
- literature disposition
- reference citation and the listing of excluded references

**Claudia Frumento**  
c.frumento@icimt.com  
**Gillian Pritchard**  
g.pritchard@sylexis.co.uk

## EMWA's medical device special interest group (MD-SIG)



The MD-SIG was founded in November 2017 in Cascais. It consists of following members:

- Chairs: Raquel Billiones and Beatrix Doerr
- Committee members: Jane Edwards, Claudia Frumento, and Gillian Pritchard
- SIG supporting members: Diarmuid De Faointe, Helen Frampton, and Iain Colquhoun

### The objectives of the MD SIG are:

- to provide a forum for EMWA members to

discuss and share information in the area of medical devices and in vitro devices

- to ensure focus is given to this rapidly evolving medical communication speciality
- to support the implementation of the new EU Medical Device Regulation (MDR

2017/745) and the In Vitro Device Regulation (IVDR 2017/746)

- to act as a resource and support group for medical communicators interested in getting into this field
- to increase the educational offerings of EMWA relevant to this field

Current and upcoming activities of the MD-SIG are:

- The EMWA Symposium on "Medical Devices

and Technologies – Emerging Opportunities for Medical Communicators" will be held on May 3, 2018.

- Medical devices has been added as an area of expertise covered by for-credit workshops under the EMWA Professional Development Programme. More workshops will be offered in future conferences.
- Raquel is presenting a webinar on medical devices in 2018.
- Claudia and Gillian are spearheading the development of a standard Clinical Evaluation Report (CER) template.
- A regular medical device section has been established in *Medical Writing*.
- Topics pertaining to medical devices will be included in the Expert Seminar Series (ESS) starting 2019.

We would like to hear your thoughts and ideas!

**Raquel Billiones**  
rbilliones@clinipace.com  
**Beatrix Doerr**  
Beatrix.doerr@gmail.com

# Getting Your Foot in the Door

## Editorial

On February 1, 2018, I had the honour of representing EMWA and my company at the Zurich Life Science Day and speak about a career in regulatory medical writing. GYFD would like to thank Anuja Neve for providing us a short overview about this day and other career events organised by the Life Science Zurich Young Scientist Network.

I would like to point you to Som Basu's feature article in this issue (see p. 64) on how PhD students acquire skillsets during their studies that can later stand them in good stead in the medical writing field.

Finally, GYFD welcomes back Sara Rubio. You have read Sara's experiences as an intern and an entry-level medical writer in two previous editions of GYFD. We are very excited to have Sara as speaker at the Internship Forum in Barcelona!

Raquel Billiones

## Bridging the gap between industry and academia – Life Science Zurich Young Scientist Network

One of the most challenging questions faced by academic life scientists at some point in their career is whether to pursue research or to look for suitable positions within industry. While the shift from academia to industry might result from a carefully thought-through process, finding the right footing can nevertheless be tricky. It was this dilemma that inspired a group of PhD students and postdoctoral scientists affiliated with the University of Zurich and the Swiss Federal Institute of Technology (ETH) Zurich to form the Life Science Zurich Young Scientist Network (LSZYSN). This network aims to bridge the gap between academia and industry; the group organises a wide range of activities to build sustainable relationships with companies operating in the life sciences and healthcare sectors.

The **Zurich Life Science Day** is the largest networking event in Switzerland organised by the LSZYSN and is attended by over 600 young talented scientists and over 20 companies. This event serves as a great platform as one gets to learn about the job opportunities available at the participating companies, interact with their representatives, and hear about the job market. The companies represent themselves either via an exhibition booth and/or via talks that are a part of two parallel sessions. Each year, the network comes up with

new themes and tries to provide the attendees with as much exposure as possible to the different career options available. Many life scientists who were able to establish their professional networks through this event have now found suitable positions within industry, which is an indication of the success of this programme.

The aim of the **Career Chats** event is to invite company employees for a talk about their career path(s). We want the audience to learn from the experience of the speakers, understand the different career options available, and gain insight into how to make the transition from academia to industry. We encourage the speakers to give advice, share their personal experiences, and describe their current role and the work culture where they are employed. Sometimes the speakers are accompanied by human resource specialists who give information about job openings, application procedures, and other company background.

**Company Visits** is

So, if you are unsure about the direction your career should follow or if you are confused about the job positions you are suited for, then attend one or all these network events.



## SECTION EDITOR



Raquel Billiones

RBilliones@clinipace.com

another event where we organise a group of about 20 people for a tour within the campus of industries based around Switzerland; recently, we have also visited Germany. Our network aims to have three to four sessions of **Chats** and **Visits** from different companies within a year.

It's a given that networking plays an important role in getting one's credentials noticed. However, presenting yourself with confidence and selling your curriculum vitae can be quite challenging. Keeping this in mind, we also organise the **Zurich Life Science Week**. Within five evening sessions, coaches from the Career Centre at the University of Zurich teach 20 participants the

basics of career management and the

dos and don'ts of job interviews. They also provide insight into hidden labour markets and give information on to how to successfully apply for a job. At the end of the week, the participants, together with the coach, can work out the first steps that need to be taken towards their self-directed career.

**Mindset** is another event that entails a panel discussion by experts in the field on social and scientific issues existing in today's society.

So, if you are unsure about the direction your career should follow or if you are confused about the job positions you are suited for, then attend one or all these network events. We cover a wide range of topics such as consulting, scientific communications, regulatory affairs, medical affairs, and clinical research. Sign up for our newsletter <http://www.lifescience-youngscientists.uzh.ch/en/Newsletter.html> to stay up-to-date with all the events planned for this year. Together we can open new avenues for building and shaping our career.

**Anuja V. Neve, PhD**  
University Children's Hospital  
University of Zurich, Switzerland  
[anuja.neve@lszysn.ch](mailto:anuja.neve@lszysn.ch)

# Entering medical communications as a non-native English speaker

The third EMWA Internship Forum will be held on May 3, 2018 at the forthcoming spring conference in Barcelona. As the language of international medical communications is almost exclusively English, have you ever wondered what it takes for a non-native English speaker to break into the field?

Forum attendees will have the opportunity to

meet with companies offering internships. We are also pleased to announce that Sara Rubio will be giving a presentation on her experiences on finding employment in medical communications as a non-native English speaker. Born and raised in Barcelona, Sara speaks Spanish and Catalan as native languages. She participated in the first EMWA Internship Forum in 2016 and

completed an internship at Costello Medical. She is currently a medical writer at XPE Pharma & Science.

**Derek Ho**  
EMWA Internship Forum Chair  
University of Helsinki  
derek.ho@helsinki.fi  
internship@emwa.org

## Updated ICMJE recommendations:

### Changes to clinical trial registration and data sharing practices

The recommendations set by the International Committee of Medical Journal Editors (ICMJE) are designed to guide authors, editors, and others through all stages of creating and distributing accurate, clear, reproducible, unbiased medical journal articles. As such, they are a go-to resource for answering questions and solving issues that arise when preparing scientific manuscripts.

At the end of 2017, the ICMJE updated the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.<sup>1</sup> The most substantive updates to the recommendations are in their policy for clinical trial registration.

To start, authors are now asked to ensure they have met the requirements of their funding and regulatory agencies for reporting aggregate clinical trial results in clinical trial registries. Even when this is not required, reporting results in registries is strongly encouraged. The updated recommendations emphasise making clinical trial results publicly accessible for all clinical trials. They also now state that it is the responsibility of authors, and not the journal editors, to explain any discrepancies between results reported in registries and journal publications.

The ICMJE's guidelines for clinical trial registration now also include a new data sharing policy:<sup>2</sup>

1. *As of July 1, 2018, manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement (see below).*

2. *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 registration this should be reflected in the statement submitted and published with the manuscript and updated in the registry record.*

The data sharing statements must indicate:

- whether individual de-identified participant data (including data dictionaries) 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;
- by what access criteria data will be shared (i.e., with whom, for what analyses, and how).

Usefully, the updated recommendations provide a table with examples of data sharing statements that fulfil the new requirements.

Authors of secondary analyses using shared data must now attest that their use was in accordance with the terms (if any) agreed to upon their receipt and must reference the dataset identifier. They must also explain completely how their analyses differ from previous analyses and are encouraged to collaborate with, or at least fully acknowledge, those who collected the data.

The updated recommendations also include a revised section on predatory and pseudo-journals – journals that claim to be scholarly medical journals yet do not perform peer review and charge (often hidden) fees for article processing and publication.<sup>3</sup> The revisions give

details on how these entities operate and provide guidance and resources for identifying and avoiding them.

Finally, the ICMJE recommendations now set in stone that *all* investigators are responsible for ensuring the planning, conduct, and reporting of human research are in accordance with the revised 2013 Helsinki Declaration and that all authors seek approval to conduct research from an independent local, regional, or national review body (e.g., ethics committee, institutional review board). These commitments to protecting research participants must be stated in the manuscript's Methods section.

**Jonathan Pitt**  
jpitt@4clinics.com

### References

1. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. December 2017. International Committee of Medical Journal Editors. Available from: <http://www.icmje.org/recommendations/>.
2. Taichman DB, Sahni P, Pinborg A, et al. Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors. *Ann Intern Med.* 2017;167:63–65.
3. Identifying predatory or pseudo-journals. 18 February 2017. World Association of Medical Editors. Available from: <http://www.wame.org/identifying-predatory-or-pseudo-journals>.





# Out on Our Own

## Editorial

Greetings, readers! In this edition of *OOOO*, we have three splendid articles.

One of the main reasons why the Freelance Business Group (and the whole of EMWA as well) is thriving and growing is because of the number of our members who volunteer to carry out our activities and help in implementing new initiatives. Becoming a Table Leader (TL) at the Freelance Business Forum (FBF) that is held at every EMWA conference is a fantastic opportunity for our freelance members to indulge in and promote networking and interpersonal communication. The TL's task involves moderating a topic while facilitating and encouraging participation from those at their table. Given that the Table Discussion session is a high-demand event at the FBF and taps a collective response to issues pertaining to the freelancing business, the help rendered by the TLs is of immense value. While TLs are usually senior and experienced freelancers, at the recent conference in Cascais, Portugal, no

less than three TLs were new to freelancing and even EMWA. Two of these, Irene Farre and Laura Kehoe, share with us their thoughts on volunteering as TLs at the FBF and their experience with the conference as a whole.

Getting out on our own, hanging up one's shingle, becoming a businessperson, becoming a freelancer—it is really an adventure, it seems sometimes. To give up a steady 9-to-5 with an assured paycheck at the end of month, or even careers in the pharma industry or academia or anything mainstream, to work out of one's spare room or even on a sofa, shuttling between being a CEO and a janitor, it can't be anything but an adventure. But that is how all of us have embarked on this adventure: with an equal measure of trepidation and bravado, uncertainty and resolve. In her article, Lisa Diamond, a freelance medical writer and medical advisor from South Africa, tells us her story about how, after a gruelling stretch in medical studies, she decided to become a medical writer and how EMWA helped her get underway. After 15 years

as a professional psychiatry nurse in the UK, Emma Vinton thought that she could better utilise her experience by becoming a medical writer, especially because she understood the patient-centric nature of our job. In her article, Emma shares with us how she plans to develop a career in medical writing and also help in mentoring other medical writers who do not have a clinical background.

As a volunteer editor of *OOOO*, one of my biggest joys is helping in bringing the stories of our members, and sometimes guests, to all. These stories served as a source of information as well as inspiration well before I began my freelancing adventure 2 years ago, and they continue to do so today. I hope that these are as beneficial and motivating to you. I'd like to thank Irene, Laura, Lisa, and Emma for their contributions. I'd also like to thank my fellow FBG subcommittee member, Paul Wafula, for his help with putting this issue together.

Happy reading!

Satyen Shenoy



## The Freelance Business Forum in Cascais: Thoughts from our newbie table leaders

One of the main goals of the Freelance Business Forum (FBF) – a hot ticket event at EMWA conferences – is to encourage interaction between our freelance members, especially those

who are new to EMWA or the world of freelancing in general. And given its informal and unstructured nature, the hour-long Table Discussion session of the FBF is the perfect

opportunity to do so. Each table comes with a Table Leader (TL), a volunteer who initiates and moderates the chitchat at their table, makes it participatory for all others around their table, and

moves the conversation along. As daunting as most attendees presume being a TL to be, almost all claim to have enjoyed the experience.

At the recent conference in Cascais, some of these newbies went a step further and agreed to volunteer as TLs for the FBF. Here two of the TLs, Irene and Laura, share their thoughts with us.

## **Irene Farre** IF Medical Writing, France

One of the contacts I made at my very first EMWA conference in Birmingham encouraged me to become a TL at the FBF at the Cascais event. I must admit that he did not have to insist a lot. From the beginning, I thought it was a fantastic opportunity to network with other freelancers and to talk about the joys and struggles of having your own business. In this short article I will share what I have learnt about being a TL.

For those of you who are not familiar with the concept, at the end of the FBF, various subjects are discussed by smaller groups of attendees around tables, hence, Table Discussions! You can

decide which table to join and even swap tables if you think that you have received all the information you were after. Indeed, the discussions are unstructured and less formal, which allows interaction and reflective thinking amongst the members.

At the beginning, the thought of being a table leader was a bit daunting. I did not consider myself to be an expert in any of the potential topics proposed for the FBF, nor did I have a long working experience as a freelancer. How was I going to do it? Thanks to Satyen, a member of the Freelance Business Group (FBG) subcommittee, I understood that the role of a TL was actually to be a facilitator: helping everyone to express his/her point of view on a certain subject, keeping discussion focused, raising questions, and moving things along when discussion gets bogged down.

At my table, we talked about liability insurance and, more generally, about legal protection and clauses to be included in our quotations and invoices. A rather tough topic for a Friday night, but at least we got free drinks to make it easier! The whole experience was really enjoyable. Everyone contributed, and the

conversation was fluid and energetic. Producing a summary of the key points for presentation at the end of the event was a bit challenging, but it was indeed very good practice for my communication skills.

As freelancers or business owners, it's all too easy to get caught in the trap of "working *in* the business, not *on* the business". We spend all of our time working for our clients, but very little time looking at the big picture or asking important questions. The FBFs at EMWA conferences are a fantastic way of breaking this habit and encouraging you to start working on your business. Moreover, you can meet like-minded individuals, people you can work with or learn from in some way.

If you are an independent worker (freelancer, consultant) or running a small business, I really think you will get a lot from it. One thing is for sure, I will volunteer again at the next event in Barcelona, even with more reason since it is my home city. I hope to see you there!

**Irene Farre**  
irene@if-medical-writing.com

## **Laura Kehoe** Medical and Scientific Copyeditor & Writer, Switzerland

The 45th EMWA Conference in Cascais, Portugal, was my second EMWA conference. However, I was approaching this one with a very different perspective and aims compared to my first one. The first one I attended, in Brussels, was when I was working as an editor for a medical journal. I followed courses that were related to the work I was doing and perhaps that my boss would approve of. Life has changed since then, and I recently decided to go out on my own and become a full-time freelance medical writer. Therefore, the course choices were mine, and I wanted to benefit from everything I signed up for.

Thinking of the direction I wanted to take for my freelance work, I signed up for two interesting workshops. I also put my name down for the seminar – Introduction to Medical Writing – and the Freelance Business Forum (FBF). A week before the conference, I received a motivating and interesting offer from Satyen, a member of the FBG subcommittee, which is the group of volunteers who organise the FBF. He asked me if

I would be keen to be a table leader (TL) for the FBF. Initially, I was thinking "What can I offer to the people attending the FBF?". I had only been a freelancer for a couple of months so I felt inexperienced, but as I hate to turn down opportunities, I put a brave email together and responded with equal enthusiasm. It would be a pleasure. I informed him of my concerns, but he assured me that the event was to be very relaxed and he was confident that I would have a lot to offer fellow freelancers. Satyen summarised that the TLs are there to initiate a discussion, try to encourage all those around the table to participate, and to recognise when a discussion was going a bit stale to move it on.

I arrived with some ex-colleagues to the wonderful Cascais Miragem hotel. A moody rain-filled sky, and a grey turbulent sea lapping at the foot of the hotel created quite a dramatic setting for the start of the conference. Heading straight for the EMWA lunch I immediately saw a few faces from the previous meeting and

reacquainted myself with these fellow attendees. Instantly I felt that it was going to be a great conference for me. At the networking drinks events on the first evening, Satyen made his way around the large group of delegates to identify his TLs. He introduced me to a couple of other TLs, and I discovered that a few more were also new to the FBF and had never been a TL. This reassured me, and we all had a good chat about our expectations. Altogether we were about 10 TLs from various walks of life and we all had chosen from a list a few topics to discuss.

The FBF happened on Friday evening in between workshops and the social events. My initial thoughts when I signed up for the FBF was that it would be a very formal event, a list of dos and don'ts as a freelancer, and maybe a few speakers talking about how they became freelancers. But in fact, it was a pleasant surprise, and a lot friendlier and more interactive than that. Satyen welcomed the attendees and summarised what the FBF was all about. There was also a

welcome message from the EMWA President, Abraham Shevack. And then the TLs were announced along with the main topics to be discussed at their respective tables. To break the ice and get discussions flowing, drinks were served, and we went to our respective tables.

My topic was “freelancers’ dilemmas”, very apt as I was already dealing with my own challenges in going out on my own as a freelancer. A small group formed – of people that were already freelancers or people who were thinking of making this career transition. I got the discussion started with asking “how do we find clients?”. This appeared to be a common concern. We discussed using our existing network, ex-colleagues, university links, etc., as the best way to start. From there, it tends to be word of mouth, and if you’ve done a good job for one client hopefully they’ll return to you and recommend you to their colleagues. We then moved onto the subject of having access to journals that are not

open access. This was an interesting and unresolved point: when working for an association, society, pharmaceutical company etc., we have the freedom to download the articles we need to write or check facts, but when we are out on our own, how do we gain access? We discussed another dilemma: the business aspect of branding ourselves. The group next to my table, led by Mark Dyson, also a first-time TL, was discussing logos, websites, and business cards, so we decided to merge into their discussion. This is the fundamental idea behind the FBF; people are free to move from table to table, to address questions to other freelancers, and perhaps to share experiences with a group. The topics are diverse and TLs are free to let the discussion develop into a different topic if that’s the way it’s going. Drawing the event to a close, the TLs each took a turn to summarise to the whole group what was discussed at their table.

The whole experience was positive and useful.

I chatted with a lot of fellow freelancers, business cards and LinkedIn accounts were flying around, and the atmosphere was calm, relaxed, and friendly.

As freelancers, we tend to work in isolation, at home, and without a person next to us to throw an idea at. This type of event allows freelancers to connect with others who are in similar situations. Indeed, after the conference I contacted a few people to continue the discussions we started during the event, and others contacted me. It really is a community of people willing to help one another. The next EMWA conference in Barcelona is already in my diary, and I will be putting my hand straight up to volunteer as a TL if the opportunity arises, and others should do so also. Thanks to the FBG subcommittee and all other organisers and volunteers at EMWA. It was a great event.

**Laura A. Kehoe**

[laura.a.kehoe@gmail.com](mailto:laura.a.kehoe@gmail.com)

## The elusive journey from nurse to medical writer

I discovered medical writing by chance after completing a master’s degree in public health at Northumbria University. I moved to West Cumbria during my studies and worked as a community psychiatric nurse and mental health care coordinator in a busy community mental health team. However, the work became increasingly under-resourced and I felt compelled to move on. After a lot of deliberation, I decided to leave nursing and try something different. I wanted to work more flexibly but did not want to abandon the unique skill set gained during my 15 years in psychiatry. One night I searched online for the perfect job, and there it was: medical writing. The profession is unique in that many enter it by chance after working in senior medical or academic roles. Some writers have a hard scientific, lab-based background, and many have higher academic degrees such as PhDs. I consider myself to be at the opposite end of the scale. I thought my softer skill set would be disadvantageous, but it turns out that this is not the case. This article focusses on the transferable skills needed to switch from healthcare to medical writing:



*Wasdale in West Cumbria*

## Soft skills vs. hard science

It is not necessary to have lab-based skills to become a medical writer, though some biomedical experience can be useful when writing about genomic or cellular studies. I found that it is best to focus on what you know and build your knowledge around each new project. I was surprised by what I had already achieved during my time in clinical practice and started to apply everything I had learned to my new role as a writer. Nurses regularly assess, plan, deliver care, and evaluate interventions using tried and tested (evidence-based) patient outcome measures. We constantly weigh and prioritise important, sometimes conflicting information. Decisions are then made around the strength of that information. Medical writers use these analytical skills to review complex data sets and present them clearly to specific audiences. I love this aspect of the work as it helps me to maintain a sharp mind and critically assess everything I present.

Nurses are bound by the Nursing and Midwifery Code of Professional Conduct. They must be accountable for their actions and work to high standards. Medical writers must apply similar standards to their work: guides such as "Good Publication Practice 3" (<http://www.ismpp.org/gpp3>) and Elizabeth Wager's *Getting Research Published: An A-Z of Publication Strategy*<sup>1</sup> ensure that publications and company-sponsored research are presented clearly and fairly. Nurses who have completed research will be at an advantage to their peers as they will be more familiar with clinical reports, study protocols, and meeting ethical standards. A further degree such as a master's in public health, is highly recommended for clinicians wanting to transition into medical writing. It provides solid foundations in epidemiology, medical statistics, and health systems and promotes clear and logical manuscript development. Hospital libraries are easily accessible to healthcare professionals and are great sources of medical and statistical knowledge. Students in higher education can access large university medical and scientific collections. Online journals and quick-study guides are an excellent way of getting up to speed with unfamiliar disease areas and treatments. Charity websites, blogs, vlogs, and disease-specific forums are also excellent means of assessing what patients really think about conditions, drugs, and treatments Learning

about the latest developments and technologies is one of the most fascinating aspects of medical communications. No two days are ever the same and nurses are used to this high level of uncertainty and unpredictability. As your knowledge and skill base increase, you will find yourself able to tackle the most complex projects and disease areas with confidence. Peter Llewellyn (community facilitator and enthusiastic medical writing advocate; <http://www.medcommsnetworking.com/>; <http://www.nextmedcommsjob.com>) showcases some excellent online resources for those aspiring to enter the profession and, for those already working, looking for freelance projects.

## I had to become more tenacious and business focussed

Nurses are trained to be responsive to patients' needs and provide care accordingly. This translates into a very holistic approach to writing and the patient is always at the centre of every clinical trial. Nurses and other clinicians are at an advantage in that they can pick up subtle cues that may be missed by writers who have not had the opportunity to capitalise on this skill set. Mental health journal articles about communication can help to bridge theoretical gaps, but nothing beats the experience of face-to-face patient dialogue. I decided to focus on this additional layer when developing my business model. This has allowed me to create a highly personalised service for both the client and the end-user.

As a freelance business owner, you will only succeed if you are confident, tenacious, and always on the front foot. You need to constantly market yourself, read extensively, and accept new projects.<sup>2</sup> Get as much support as you can from specific medical writing organisations such as EMWA ([www.emwa.org](http://www.emwa.org)) and the International Society of Medical Publication Professionals (ISMPP; [www.ismpp.org](http://www.ismpp.org)). EMWA provides very interesting workshops and training to help newbies acquire the necessary knowledge to gain entry positions in their chosen agencies and companies. EMWA's internship programme is invaluable as it allows aspiring writers to set a foot in the industry, and a lucky few might get hired. EMWA's freelance forum is also an excellent platform for making yourself known and for securing new business. ISMPP also offers structured exams to help you get qualified.

## Marketing our unique relationship and mentoring skills:

The shift from "care provider" to "knowledge provider" is unique. It gives the medical writer special insight into patients as trial participants. Nurses spend more time with patients than doctors can, and by seeing patients at their most vulnerable they can capture those precise patient perspectives. Nurse communicators have been heavily in demand by pharmaceutical companies recently. Close relationships with carer support organisations also offer additional insights into patients' unique journeys through healthcare systems. Clients are starting to recognise the value of this special relationship, and it stands to reason that the more time one has spent with patients during treatment, the more accurately one will be able to tell their stories.

For many years, mentorship has been intrinsic to nursing practice. Diplomas are usually undertaken once nurses have completed a full year of qualified work. They entitle nurses to supervise students as long as they attend annual updates via their employer. This is being developed in medical writing and several schemes are now available via <http://www.nextmedcommsjob.com/>. However, much more needs to be done to develop mentorship, so I am calling upon clinicians-cum-medical writers to contact me with their details, areas of expertise, and any mentorship experience so we can support medical writers who do not have a clinical background. A new clinician-specific database, called Clini-KOL, is now in development. It will allow writers to conveniently connect with key opinion leaders across several clinical disciplines, and grant them access to the tools and resources previously only available to clinically-trained writers. Please contact me if you would like to get involved, and I look forward to working with you in 2018.

## References:

1. Getting Research Published: an A-Z of Publication Strategy (3rd edition 2015).
2. Kryder CL, Bass BG. The accidental medical writer. How we became successful freelance medical writers. How you can, too. Cynthia L Kryder and Brian G Bass Publications. 2008.

**Emma Vinton**  
[psylingual-medical@outlook.com](mailto:psylingual-medical@outlook.com)

## Bloody shoes to barefoot Perspectives from a South African medical writer

“I don’t want to do this anymore”, I said to Dr G. as we sat outside casualty.

“Well, the patients aren’t going to see themselves”, he replied, as I washed down a can of Coke in two swift sips.

It was 2010, and we were on call in surgery, working through the night at a rural hospital in KwaZulu Natal, South Africa. There was dried blood on my shoes, and powdery latex had caked in the webs of my fingers from the countless disposable gloves I had used over the last twenty-something hours. It had been an average Saturday night – around five serious stab wounds (one with the machete still *in situ*), a few car accident victims, a couple of upper gastrointestinal bleeds, and only one stabbed heart (much better than the three that casualty had seen the night before).

The bench of patients waiting had been cleared multiple times, only to refill within minutes. Most of this refilling was due to new accidents and emergencies, but occasionally the same patient who had been seen and discharged some hours before would reappear on the bench. One had his forehead sutured previously, and returned to the party, only to sustain further injuries in the same pub brawl.

Working in casualty was no better or worse than working in another department. In Obstetrics and Gynaecology, we cut up to ten emergency Caesarean sections in the night alone. An Orthopaedics call felt like being a tortured carpenter: forced to stand in the operating theatre for hours on end, surrounded by nails, screws, drills, and the fine dust of bone in the air. In Paediatrics, at least three children would go into respiratory distress every night, making it virtually impossible to see all 60 children in the ward and do all their blood work before the morning ward round. The children sometimes made our jobs easier by extracting their own worms from their noses or mouths or other places, but mostly they made it more difficult by repeatedly removing their drip lines or spiking temperatures or breaking our hearts when they died.

HIV/AIDS and tuberculosis lurked in every queue and every ward. Long hours in these busy hospitals make needle-stick injuries common. I took post-exposure prophylaxis after my first needle-stick injury, but I only lasted a few days before the side effects became so unpleasant that



I discontinued. I ignored the five or six needle-stick injuries I sustained subsequently, but for a silent prayer and a plan to test regularly for HIV in the future.

By the end of my 2-year medical internship, I was exhausted and sicker than I have ever been in my life. I had picked up an odd superbug from a patient in the ward, and when I saw my own chest X-ray, big tears rolled down my cheeks. I was admitted to hospital on Christmas day, six days before the end of my internship contract. From my hospital bed, I attempted to find someone to help me with my final 24-hour paediatrics call. I offered a colleague R5000 (about €500 back then, roughly a quarter of my monthly paycheck) to do the shift for me. She refused. We all hated it that much.

***“Is it really so damnably self-indulgent to want to love what you do? Life is short.”***

*Alexandra Robbins*

I already knew in my fifth and sixth years at medical school that my career choice was wrong, and had threatened to leave medicine several times before I even got my degree. My exasperated parents eventually contacted the deanery at med school and got them to sit down and talk some sense into me. I was told that I should get

through the degree, and then I could do anything I wanted.

Now, after completing my 6-year degree and my 2-year internship, I only had one more year of public service left before I could escape into private practice, the more luxurious and more lucrative world of medicine. But I didn’t want to do that. I was desperate to get out of clinical medicine altogether.

Prior to being admitted to hospital, I had spent a few months hunting for other ways to use my medical degree. I wanted to use my medical acumen in a way that didn’t involve signing death certificates, preparing rape kits for people who had been sexually assaulted, bribing laboratory staff for quick blood results, or taking anti-retroviral drugs for post-exposure prophylaxis. I Googled “What else can you do with a medical degree”. Sifting through the results, there was one job title that struck me. Medical writer. Without knowing anything about the industry or what this career involved, I decided I’d become a medical writer.

One minor problem. No one in South Africa seemed to have ever heard of medical writing, and there was no established medical writing industry. I was going to have to broaden my search. I sent over a hundred emails, mostly responding to medical writer job advertisements in Europe

and the US. The response was uniform: “Yes, you’re a doctor, and you can write. But you have no experience, and you’re in Africa, with a passport that doesn’t get you very far. So best of luck.”

***“If you want to live an extraordinary life... you’ll eventually have to start considering all the possibilities, not just the ones made convenient by society.”***

Tynan

Back to the drawing board. I needed to find a job where location and geography weren’t an issue. I wanted to be able to work from anywhere and everywhere in the world, without ever wearing shoes. Seemed like a pipe dream, but I was moments away from making the best decision of my life. I was also moments away from discovering the European Medical Writers Association.

And there it was. A job ad on the EMWA job board, for a remote medical writer. The company was a small medical communications agency in Europe. I interviewed on Skype, without wearing shoes. I was asked to provide a writing sample, which I worked on barefoot. The piece was about how the pen is mightier than the stethoscope. I got the job.

Exactly one month after my internship had ended and I had been discharged from hospital, I started my first day as a medical writer, sitting on a balcony near a beach in Koh Lanta, Thailand. I was tasked with revising a diabetes manuscript, but I didn’t even know how to work the comment and tracking functions in Microsoft Word, let alone use referencing software. Confidence intervals and *P*-values were a distant memory; they had only been covered for about 30 minutes during the 6-year medical degree, and we hardly cared about them as young clinicians. I had hundreds of pages of source data that I needed to use to address myriad comments on niche super-specialized topics in diabetes and it felt like only the insulin molecule itself could understand.

The learning curve didn’t scare me. With reasonable mental faculties and a good wi-fi connection, you can teach yourself almost anything, and you can do great work. I was finally not only barefoot, but location-independent. In the year that I spent as a remote writer for the European company, I worked in Thailand, San Francisco, Las Vegas, Philadelphia, Indonesia, Johannesburg, Cape Town, and Copenhagen.

***“You can be barefoot and have worries.”***

Brigitte Bardot

Without this lucky break on the EMWA job board, I’m not sure my medical writing career would have ever taken off. But I wanted even more freedom. I wanted occasional days off to potter around and swim and read non-medical things. I wanted these days off without having to ask or tell anyone. And I wanted to be able to get on a plane whenever the urge hit. So, I resigned and bought a backpack.

It was a rash decision with no proper plan or forethought, and it didn’t work. Without a salary, travel was impossible, and the new backpack remained unused in the closet. Without a job, mental stimulation was non-existent. I made tiny scraps of money by making cupcakes for birthday parties and playing online poker. After a few months, I needed money and I needed to *do something*. I signed a contract with a medical insurance company as a consultant medical writer and found myself in a cubicle, under fluorescent lighting, with high heels on.

I did good work, and the people in the company liked me. Since they weren’t really sure what to do with me at first, I volunteered to revise their white papers, write some new ones, and even create personalized disease management programmes. Within six months I was offered a permanent position, which I accepted. Unfortunately, it didn’t last long. I was burnt out, and my mother was ill. So, I resigned for the second time and took off my shoes.

In the months that followed, my bank balance dwindled once more, and I began to seriously consider going back to clinical medicine. Fortunately, I was asked to assist with an international medical advisory board, and I was offered a fixed-term contract as a medical advisor for a health risk management company. I went back to the office world in my heels, but I only lasted two months before my mother’s health deteriorated, and I resigned for the third time in the space of 2 years. She passed away 6 weeks later. After a period of intense mourning, I took the backpack out the closet and booked a ticket to Costa Rica.

***“Two roads diverge in a wood, and I took the one less travelled by, and that has made all the difference.”***

Robert Frost

In the 3 years that have passed since my mother died, I have not returned to the hospital or to the office. I only wear shoes a few days of each month, when I have to go to meetings or conferences. I work as a freelance medical writer and medical advisor for South African and international companies. I have assessed thousands of medical cases and have provided medical expertise to multiple organisations, but I haven’t laid hands on a patient. If you combine this with the countless journal manuscripts, patient communications, and digital projects, my reach is far greater than it would have been in clinical medicine, both numerically and geographically. I may add that medical writing saves lives, as Sophia Whitman showed us in the 2017 summer edition of the journal.<sup>1</sup>

Despite it being massively rewarding on personal, academic, and financial levels; being a freelance medical writer is lonely, particularly for a South African. Nearly 6 years after EMWA landed me my first job, I attended my first EMWA conference in Cascais, Portugal. Here I found a league of accidental and intentional medical writers, each of whom had followed a unique track into the industry, and many of whom were freelancers just as eager for a coffee with a colleague as I was.

The sense of belonging and the work ethic of these EMWA members reinforced the career decision I had made all those years before. I have had an obsession with writing and research for as long as I can remember, but being a word nerd or one of those geeks who likes graphs doesn’t mean a whole lot unless you know why you’re doing it. Words matter because information matters, and information matters because people matter. Data is big and expanding in a quantum way, and it is our responsibility to use it to help people and make their lives better. If you can fulfil that responsibility barefoot from anywhere in the world and cope with the uncertainty of never having a real job, a fixed salary, or a boss – then I think you’ve got it made.

## References:

1. Whitman S. Good medical writing saves lives: the perspective of a former medic. *Med Writ.* 2017;26(2):52.

**Lisa Diamond**  
Johannesburg, South Africa  
lisadiamond308@gmail.com

# Upcoming issues of **Medical Writing**



## June 2018: **Public disclosure**

This issue will cover public disclosure and publication of clinical trial results, especially including recommendations and requirements from the European Medicines Agency. **The deadline for feature articles is March 15, 2018.**



## 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.**

### 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).



<http://journal.emwa.org/>