

Volume 26 Number 4  
December 2017

# Medical Writing

6EMWA celebrates  
25 years, 1992-2017



## Preclinical studies

### Also in this issue...

- How to survive Brexit as an independent medical writer
- Creation of a patient-centric patient lay summary in the local language
- Six communication rules for scientific presentations and writing
- So, you want to be a medical journalist?



EUROPEAN MEDICAL WRITERS ASSOCIATION



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

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# Medical Writing

## Preclinical Studies

### Nonclinical and preclinical research: A roadmap to unfamiliar terrain

Welcome to this special issue about nonclinical and preclinical research. Nonclinical and preclinical research is the first step toward new drug development, where scientists investigate mechanism of action, pharmacokinetics, and safety. Many medical writers spend their careers in the regulated world of registered clinical trials, where there are well-defined rules, endpoints, and guidelines for writing documents. To these writers, reporting the countless methods, standards, and models used in nonclinical and preclinical studies may seem complex and daunting. A writer may have to learn methodological details of X-ray crystallography, drug interaction models, genetically modified species, and cell culture. Experiments in a single manuscript may involve multiple animal models, in species that may vary from apes to mice to woodchucks to zebrafish. Guidelines for reporting these methods and models may be hard to find or nonexistent, and many journals offer only sparse reporting instructions. In other words, to a medical writer accustomed to clinical trials, reporting nonclinical and preclinical research may at first seem like the Wild West.

However, the various disciplines that make up nonclinical and preclinical research, such as toxicology, genetics, structural biology, pharmacokinetics, and pharmacodynamics have their own rules and guidelines that may be unfamiliar to members of other disciplines. Thus, behind the chaos of this Wild West is a loose structure, woven together from the threads of many disciplines. Yes, nonclinical and pre-clinical studies are often complicated, but they are integral for advancing new therapies and medications through clinical development. Clear, concise, and ethical communication



#### GUEST EDITOR



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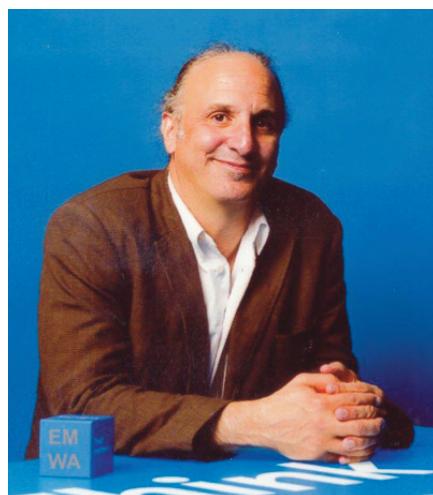
of this research can guide discovery, reduce research costs, and, perhaps, contribute its own small bit to saving lives.

This issue on nonclinical and preclinical studies begins with an article by **Jennifer Honek**. She explains the basics of drug development and the path new therapies must travel to move from bench to bedside. **Alexander Nürnberg and Hélène Pierre** introduce the growing world of nonclinical regulatory writing, explaining the distinct challenges that nonclinical research poses to the writer. **Heidi Lightfoot** argues for clear and routine reporting of all research, whether the outcome is positive or negative, and **Sandra Tillmann** uses practical examples to explain the importance of clear and concise methods in animal experiments. **Laia Pedro-Roig and Christoph H. Emmerich** follow with an article about the economic and scientific impact of the reproducibility crisis, offering practical solutions for improvement in preclinical research. Finally, **Anna Buryakina and Natalie Merkulova** cover problems and caveats associated with regulatory documents and preclinical studies in Russia.

In addition to nonclinical and preclinical studies, this issue also has articles on other topics. **Ben Rogers, Jonathan Oliver, and Elsa Lewis** offer advice on surviving the Brexit as a medical writer. **Satoru Mogami and associates** report research on designing patient lay summaries for Japanese audiences. **Christian Kressmann and Stefan Lang** follow with an article about presenting and writing about science. Finally, **Claire Hawksworth and company** discuss the differences between medical writing and medical journalism.

To a medical writer accustomed to clinical trials, reporting nonclinical and preclinical research may at first seem like the Wild West.

# President's Message



## Dear EMWA Members,

The time has been passing so quickly, with 2017 coming to an end and the holiday season now upon us.

I am sure we all have enjoyable memories of our very successful conference in beautiful Cascais.

Since my last message, the Executive Committee has been quite busy planning our annual Spring Conference in Barcelona, May 1–

5, 2018. Speakers are currently being lined up for the symposium on medical devices and we have now organised four Expert Seminar Sessions covering both regulatory and medical communications topics.

You have already been receiving the EMWA News Blast since September. These are monthly newsletters that we have been preparing featuring short digests of current news items about our conferences, webinars, and information that we think will be of general interest to most of you. Since these are abridged articles we also provide links to the EMWA website to find out more. We hope that you have been enjoying these newsletters. Please contact our Public Relations Officer, Maria Almeida, if you have any newsworthy items to submit or if you have any feedback.

In other news, we have translated the Joint Position Statement on the Role of Medical Writers in preparing scientific manuscripts into German, Italian, French, and Spanish and have posted these translations on the EMWA website. Our aim by doing this is to spread the word to non-native English speakers. Our colleagues in the American Medical Writers Association and

the International Society for Medical Publication Professionals are also informing their members about the translations as they appear on our site. The translations have been posted each month since September; the Spanish translation is due for publication in December.

The raw data from the EMWA salary survey (the last one was published in 2012) are currently undergoing evaluation, with the results expected to be published in the March issue of *Medical Writing*.

Our webinar programme continues to host engaging presentations with topics including writing clinical study reports for medical devices, new regulations governing medical devices, information regarding patient registries, practical tips for project management, and the first steps to launch a freelance business. New webinars are being planned for 2018, so please check the EMWA website for dates and times.

We hope you enjoy reading this issue of *Medical Writing* dedicated to preclinical studies, and we would like to wish you all happy holidays and the best of luck in the New Year.

**Abe Shevack**

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# Save the date

The 46th EMWA Conference in  
**Barcelona, Spain**

May 1-5, 2018

Featuring a symposium on medical devices

# EMWA celebrates 25 years



As recounted by past President Geoff Hall in the March 2008 issue of *The Write Stuff*, EMWA got its start in 1992, when the first formal meeting was held in Brussels.<sup>1</sup> This first meeting was quite small – only 32 people attended – and there were no workshops. EMWA actually started out as a chapter of the American Medical Writers Association but struck out on its own in 1997.

So much has happened over the years. In 25 years, we have grown from those first 32 attendees and annual meetings with no workshops to more than 1,000 members and bi-annual meetings with more than 130 active workshops plus symposia at spring conferences. EMWA is more dynamic than ever thanks to a large group of volunteers and an excellent Head Office.

Here are some of our main accomplishments since Geoff Hall wrote his article in 2007:

- Instituted 5-year plans to prepare for EMWA's future and better represent members' needs
- Moved from in-house volunteer management to professional management and moved the headquarters from Switzerland to UK. These transitions were definitely not easy, but

thanks to the efforts of many EMWA volunteers and our current management company, things are going very well.

- Became recognised as the principal representative of professional medical writers, including participating in Good Publication Practice Guidelines, organising the CORE Reference, and preparing with ISMPP and AMWA the Joint Statement on the Role of Professional Medical Writers
- Expanded the Executive Committee to include Public Relations and Conference Director officers
- Created an Educational Committee to manage workshops
- Modernised and elaborated the EMWA website
- Created a Social Media Team
- Established the Geoff Hall Scholarship for new medical writers
- Stabilised the finances of EMWA
- Instituted webinars
- Created the Freelance Forum
- Moved EMWA's journal from a small in-house publication of a few pages to a dynamic

and professional format with a full Editorial Board; made feature articles open access

- Expanded the reach of EMWA outside of Europe and built relationships with other professional organisations
- Created the Expert Seminar Series and Special Interest Groups
- Created the Internship Forum

So much more can be said. We have an excellent and dynamic volunteer organisation that is constantly striving to improve and better serve our members. More on our history and progress will be coming in the March 2018 issue of *Medical Writing*, so stay tuned!

## Abe Shevak

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# EMWA News

## Editorial

The 45th EMWA Conference in Cascais, Portugal, has recently finished and we are all waiting for the upcoming annual event in Barcelona, Spain, next Spring. In the meantime, the Executive Committee is working hard on improving what EMWA has to offer to its members. In this section, our new PR officer Maria Joao Almeida will tell you more about the recently implemented News Blast, and our web manager Diarmuid De Faoite brought back the webeditorials with many interesting contributions by our members. Finally, I would

like to mention that our conference director Slavka Baronikova has been organising the 6th EMWA symposium that will take place on May 3rd, and the 4th Expert Seminar Series (ESS) on May 2nd and 4th, 2018, in Barcelona. The symposium will focus on medical devices in general, recent changes in 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

## SECTION EDITOR



**Evguenia Alechine**

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companies, patient representatives, and reimbursement professionals. The ESS will be focused on regulatory, orphan drugs and rare disorders, pharmacovigilance, and medical journalism. Don't miss this unique opportunities!

**Evguenia**



## EMWA News Blasts

The EMWA News Blasts is looking for your collaboration! In our continued efforts to provide our members with well vetted and relevant information, we have started sending out short EMWA News Blasts via email announcing important information on conferences, webinars, special interest groups, the freelance business forum, the internship forum, and other general information of interest to our members.

If you have any information for an item in the news blast, please send it to [pr@emwa.org](mailto:pr@emwa.org) by the third Friday of each month. Together with our Head Office we will compile the News Blast for distribution by the start of the following month. Please put a note in your calendars because reminders will not be sent out each month!

We appreciate your participation. Please contact us if you have any questions!

**Maria Joao Almeida**

PR Officer

[pr@emwa.org](mailto:pr@emwa.org)

## Webeditorials are back!



With the newly improved website in place (see the last issue of *Medical Writing* for details – or better yet, just visit [www.emwa.org!](http://www.emwa.org/)), attention has turned to improving the content available there. In order to offer visitors access to content only available online, the Webeditorial section has been reactivated after a hiatus of several years.

What is a webeditorial? As the name suggests, it is an opinion piece published online that touches on a topic related to medical writing. It may be serious or light, descriptive, or opinion led.

The first webeditorial since the reboot was penned by Jane Edwards and examined the impact of the new Medical Device Regulations on medical writers. You can read this as well as many other previous entries at the webeditorial archive. From the home page just navigate to About Us → EMWA News → Webeditorials.

We would like to keep this section alive with new content. This is where you come in. If you have something you would like to get off your chest about any aspect related to medical writing, please do get in touch about writing a webeditorial. Contact [webmanager@emwa.org](mailto:webmanager@emwa.org)

with your suggestion for a topic or even your finished text!

We are looking forward to receiving your webeditorials, as well as any other EMWA website suggestions and contributions you might have.

**Diarmuid De Faoite**

EMWA Web Manager

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## Zurich Life Science Day

EMWA will be represented by Raquel Billones at the Zurich Life Science Day on Thursday, February 1, 2018, at the University of Zurich Irchel Campus. Raquel will speak about careers in science writing. The event is organised by Life Science Zurich Young Scientist Network (LSZYSN), a non-profit organisation established and run by a group of graduate students and postdocs of the University of Zurich and the Swiss Federal Institute of Technology (ETH).

# Preclinical research in drug development

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## Abstract

The process of developing a novel drug is time consuming and costly. To increase the chances of successfully completing a clinical trial leading to the approval of a new drug, the choice of appropriate preclinical models is of utmost importance. Identifying a safe, potent, and efficacious drug requires thorough preclinical testing, which evaluates aspects of pharmacodynamics, pharmacokinetics, and toxicology in *in vitro* and *in vivo* settings. Nevertheless, merely a small fraction of investigational new drugs tested in clinical trials after passing preclinical evaluation eventually lead to a marketed product. Hence, there is a need for optimising current standard preclinical approaches to better mimic the complexity of human disease mechanisms.

## From bench to bedside – the long journey from the lab into the clinic

Developing a novel drug is an interdisciplinary endeavour involving a multitude of competences from biologists, chemists, computer scientists, medical staff, statisticians, and regulatory experts. Taking a compound from bench to bedside requires up to 12 years at an average estimated cost exceeding US \$1 billion.<sup>1</sup> Figure 1 summarises this long-term process (see overleaf).

Drug development starts with the identification of a “druggable” target. Bioinformatics, genetic association studies, and phenotype screening are valuable tools in the discovery of novel targets. To validate the relevance of the identified target for a particular disease, studies are performed to investigate whether target modulation is disease modifying.<sup>2</sup> Eventually, lead compounds are obtained and their potential to interact with the target as well as their effect on the biological system is evaluated. Thousands of modifications and variations of these lead compounds are synthesised and tested during preclinical activities. Once an optimised compound is identified, this investigational new drug (IND) becomes a candidate for clinical trials involving human subjects.

Clinical trials are conducted over different phases (Phase I-IV), starting from a small number of subjects and extending to large

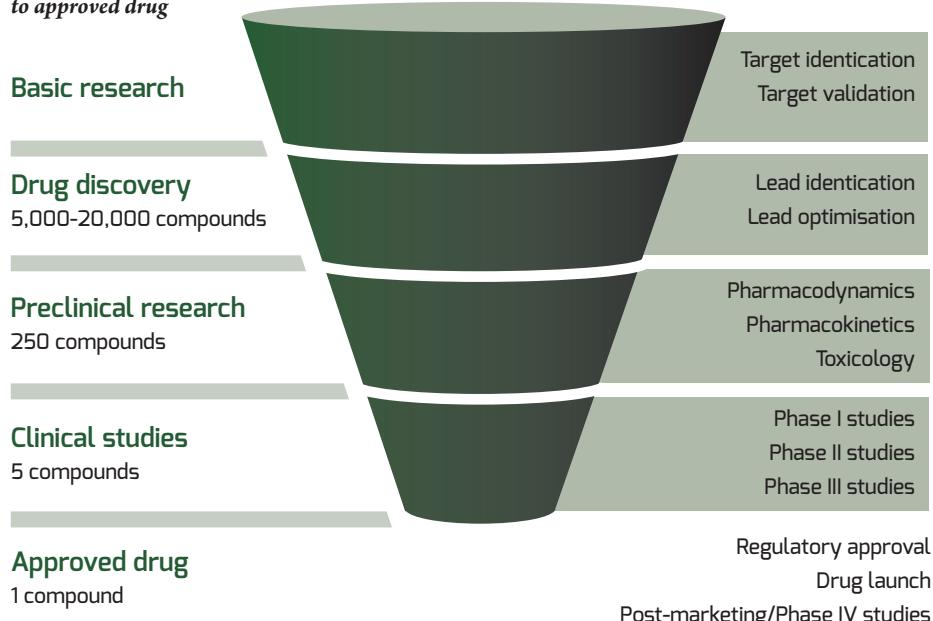
cohorts.<sup>1</sup> In Phase I studies, the IND is administered to humans for the first time.<sup>3</sup> Early Phase I studies (previously Phase 0) describe first-in-human studies where a small group of subjects, usually 10 to 15 individuals, received a single, sub-therapeutic dose to obtain pharmacokinetic information without inducing pharmacological effects. The goal of these exploratory studies is to investigate whether the drug candidate performs as expected based on preclinical studies. If successful, further studies assess safety and tolerance of the IND in human subjects. These studies typically involve 20–50 healthy volunteers. Apart from determining the drug’s maximum tolerated dose by increasing the treatment dose until dose-limiting toxicity is reached (dose escalation), the drug’s most common and serious adverse effects (AEs) as well as pharmacological, pharmacodynamic, and pharmacokinetic properties are evaluated.<sup>4</sup>

Approximately 70% of drug candidates move from Phase I to Phase II, in which therapeutic efficacy of the IND in patients is assessed.<sup>5</sup> Phase II studies typically involve several hundred patients. The study population is well defined by inclusion and exclusion criteria, and based on the dose or dose range determined in Phase I, dose response in patients and the drug’s biological activity are evaluated. Comparison of

(i) pre- and



**Figure 1. From basic research to approved drug**



post-treatment status of patients and (ii) response of patients receiving IND and a placebo drug provide preliminary data on effectiveness. Although researchers obtain indications regarding the drug's benefit, Phase II studies are not comprehensive enough to provide sufficient evidence. During Phase II, subjects are carefully monitored for AEs to further assess safety of the drug. Moreover, these trials commonly determine the optimum dose regimen to be used in Phase III.<sup>4,6</sup>

About one-third of tested INDs transition into Phase III having 100–500 patients and with the primary objective of confirming the therapeutic benefit of the IND as well as its safety and efficacy in the intended indication.<sup>4</sup> Moreover, the use of different dosages and study populations and combination with other therapeutic agents are investigated to provide information regarding indications and contraindications as well as dose range and AEs. As Phase III studies include a larger cohort and have a longer duration than Phase I and II studies, they can potentially reveal rare and long-term side effects. Based on the outcome, 25% to 30% of INDs progress to the next phase.<sup>6,7</sup>

Phase IV studies are long-term and typically conducted after regulatory agency approval (post-marketing studies).<sup>6</sup> They often involve more than 10,000 individuals of the relevant patient population and aim at gathering additional information on safety, efficacy, and new indications. Thus, Phase IV trials assess the drug's real-world effectiveness in an extensive

cohort and provide the opportunity of detecting unique AEs. In some cases, this might result in withdrawal of the drug from the market or restriction to particular uses. On the other hand, Phase IV studies may also open up new markets by demonstrating effectiveness for new indications.<sup>6,7</sup>

## Preclinical studies

Preclinical studies aim at providing information about safety and efficacy of a drug candidate before testing it in humans. Furthermore, they can provide evidence for the compound's biological effect and usually include both *in vitro* and *in vivo* studies. Preclinical studies have to comply with the guidelines dictated by Good Laboratory Practice to ensure reliable results<sup>5</sup> and are required by authorities such as the FDA before filing for approval as IND. Insights into the compound's dosing and toxicity levels are essential to determine whether it is justified and reasonably safe to proceed with clinical studies and are provided by studies on pharmacokinetics, pharmacodynamics, and toxicology.<sup>5</sup>

## Pharmacodynamics – what does the drug do to the body?

Pharmacodynamics describes the relationship between the concentration of a drug in the body and its biological effect (dose response). This includes addressing the question, how potent and efficacious the drug is with regard to its desired pharmacological effect, including safety aspects and AEs. Thus, pharmacodynamics establishes

the therapeutic index of a drug, describing the ratio of the dose causing toxicity and the dose eliciting a therapeutic effect. Ideally, the therapeutic index is large to indicate a wide therapeutic window.<sup>1</sup>

## Pharmacokinetics – what does the body do to the drug?

The effect of a drug is determined by the amount of active drug present in the body particularly at the target site. This, in turn, depends on absorption, distribution, metabolism, and excretion (ADME) of the compound. Pharmacokinetics describes changes in plasma concentrations over time as a consequence of ADME. ADME profiling is critical for establishing dose range and administration schedule for subsequent phases of the clinical trial.<sup>1,8,9</sup>

Most drugs are administered orally and need to be absorbed in the gastrointestinal tract to enter the bloodstream, allowing them to be transported to their site of action. On its way to the target site, the drug reaches the liver, where first-pass metabolism takes place. Consequently, the drug concentration – and thus its bioavailability – is reduced before entering systemic circulation. Intravenous drug administration bypasses the first-pass effect, resulting in greater bioavailability. Once in the circulation, the drug is transported to different tissues. Distribution of the compound throughout the body is determined by (i) the drug's affinity for plasma proteins, (ii) the drug's molecular properties and polarity, and (iii) tissue vascularisation. After entering the body, drugs are metabolised to facilitate elimination. Metabolism refers to the chemical alteration of the parental drug into pharmacologically active or inert metabolites. To ensure adequate long-term dosing and appropriate steady-state concentrations of the drug, it is critical to obtain information on drug elimination from the body (clearance). Clearance is mainly achieved via the renal and hepatic routes; however, pulmonary clearance plays a major role for volatile drugs such as anaesthetics.<sup>1</sup> Concomitant disease, lifestyle factors, and patient's age can affect clearance and these are frequently studied in later stages of the clinical trial.<sup>8</sup> When the rate of clearance equals the rate of absorption, a so-called steady state is reached. Typically, maintaining a stable steady state level is desirable and can be achieved through repeated dosing. Eventually, the drug

and its metabolites are excreted from the body mainly through urine or faeces.

#### Toxicology – it is potent, but is it safe?

To determine whether a drug is safe for testing in human subjects, preclinical toxicology studies are performed to identify the treatment regimen associated with the least degree of toxicity and thus determine a suitable and safe starting dose for clinical trials. Additionally, they can be used to establish biomarkers for monitoring potential AEs later. Starting with single-dose studies to identify organs that might be subject to drug toxicity, preclinical *in vivo* studies continue with repeated-dose approaches. The treatment regimen ideally mimics the intended clinical design with respect to treatment duration, schedule, and route of administration. Other studies evaluate carcinogenicity, genotoxicity, and reproductive toxicity. While the drug's genotoxic effect is usually studied based on its potential to induce mutations in yeast-based *in vitro* systems, carcinogenicity and reproductive toxicity studies typically involve rats. As the tumorigenic effect of a drug may only become evident after prolonged exposure, carcinogenicity studies comprise continuous drug administration for a minimum of six months.

### The ideal preclinical model accurately mimics human disease

Obtaining relevant results from preclinical studies with a high degree of generalisability requires appropriate preclinical models that are as comparable to the target population as possible. Typically, this involves a series of experiments using *in vitro*, *in vivo*, and more recently, also *in silico* models.

#### *In vitro* models – studying the drug in a petri dish

*In vitro* studies are a relatively fast, simple, and cost efficient way of preclinical testing. Those studies utilise cell, tissue, and organ cultures, or focus on particular cell components such as proteins or other biological macromolecules. *In vitro* studies permit tight control and monitoring of experimental settings and often provide mechanistic evidence for the investigational compound's mode of action. While having the potential to provide mechanistic insights, *in vitro* models are constrained by the fact that isolated cells may not behave in a petri dish as they would



within the body where they partake in crosstalk and interaction with millions of other cells. Consequently, more sophisticated preclinical models are required to establish the investigational compound's safety profile before transitioning to a clinical setting.

#### *In vivo* models – is the mouse the best experimental animal?

*In vivo* studies consider the complete organism based on various animal models. Similar to studies in humans, animal testing is tightly regulated in most countries and permission from local ethical review boards is required to ensure that no unnecessary harm is done to the experimental subjects. Recent advances have refined the use of animal models in drug development through non-invasive imaging technologies, microsampling, and telemetric monitoring.<sup>10</sup> Naturally, controlling experimental settings is far more complicated for *in vivo* studies and, due to the complexity of the living organism, compounds may behave differently from what is expected based on results obtained in a test tube.

The choice of appropriate animal models depends on myriad criteria and requires understanding of species-specific physiology and similarity with regard to the target organ, metabolic pathways as well as financial, regulatory, and ethical considerations. Typically, *in vivo* studies are performed in a rodent (e.g., mouse, guinea pig, hamster) and non-rodent model to comply with FDA requirements. Mice, rats, and dogs are among the most frequently used animal models while testing in primates (e.g., monkeys, apes, etc.) is performed occasionally and typically for larger molecules.<sup>9</sup> One of the most popular animal models in

pharmaceutical testing is the mouse.

The genomes of mouse and man are highly similar: 99% of all mouse genes overlap with those of humans. Additionally, genomic manipulation in this organism has become fairly simple. Nevertheless, species-specific differences in host immune response, drug metabolism, and tumour heterogeneity affect therapeutic outcomes. Differences in pharmacokinetics and pharmacodynamics among species are also not negligible and thus, mouse models often suffer from poor predictive power regarding clinical efficacy.<sup>11</sup> However, lack of superior alternatives makes mouse models the gold standard for testing cancer-targeting drugs.

Classically, such mouse cancer models were limited to transplantation of cultured human tumour cells (cell lines) to immunodeficient mice such as nude or severe combined immunodeficiency (SCID) mice.<sup>12</sup> Transplantation of cells, tissue, or organs from one species to another is called xenografting. In these cell line-derived xenograft (CDX) models, cancer cells are injected subcutaneously and tumour growth curves are established by measuring the size of the tumour in regular intervals. Treatment of tumour-bearing mice with a drug candidate provides information regarding its potential to reduce tumour growth and thus its *in vivo* efficacy. However, these cell lines have been passaged under artificial conditions that do not recapitulate the natural tumour microenvironment. Consequently, CDX models may lack similarity with human disease.<sup>11,13</sup> To improve clinical relevance, a range of different mouse models has been developed and is used in *in vivo* experiments:

- Patient-derived xenograft (PDX) models: Tissue from a patient's primary tumour is directly implanted into the animal. This strategy omits *in vitro* adaptation of tumour cells and, thus, these models are more similar to human disease in terms of stromal composition and tumour heterogeneity, in contrast to classical CDX models. The PDX approach is challenging; however, recent advances in sample retrieval and transplantation technology made this method feasible. To date, PDX models consist of almost exclusively subcutaneous transplants.
- Orthotopic tumour models: Tumours are implanted into the organ of origin (i.e. orthotopically) to better mimic the microenvironment and recapitulate metastasis

pathways of human tumours.<sup>11,13</sup> Consequently, orthotopic models are more clinically relevant. Orthotopic PDX models are technically challenging and thus uncommon, while orthotopic transplantation is widely used for CDX models.<sup>11</sup>

- Genetically engineered mice (GEM): Genetic engineering has given rise to humanised mouse models and provides valuable tools for translational research. Through genetic manipulation, mutations in oncogenes or tumour suppressor genes associated with human malignancies are introduced. In GEM, tumours develop orthotopically from initiation through progression in their native microenvironment recapitulating human tumourigenesis.<sup>11</sup> Hence, preclinical studies in GEM have the potential to provide more relevant data for subsequent clinical trials.

#### *In silico* models – the computer's role in drug development

Progress in bioinformatics over the past decades has made *in silico* studies attractive so that they often precede or complement *in vitro* and *in vivo* studies. *In silico* models are based on computer simulations and provide information on how an investigational compound might behave in subsequent *in vitro* and *in vivo* experiments.<sup>14</sup> Apart from technological requirements, these computer simulations demand expert knowledge in biochemistry and molecular biology.

#### Preclinical research is indispensable

Despite all efforts to identify relevant animal models to ensure a significant translational value, drugs often show different pharmacodynamic characteristics when administered to human subjects. Thus, merely one out of five investigational drugs tested in clinical trials eventually gains approval for clinical use. Some studies even report that only nine percent of compounds passing preclinical efficacy

evaluation are approved by the FDA.<sup>11</sup> The fact that most anti-cancer drugs do not pass efficacy evaluation in Phase II and III studies suggests that currently used preclinical models fail at appropriately mimicking tumour heterogeneity, host factors, and drug resistance mechanisms.<sup>15,16</sup> Nevertheless, preclinical research is indispensable to protect human subjects in clinical trials. Adequate design of preclinical studies and careful choice of model systems are vital to ensure relevant results that translate into applicability in clinical settings.

#### Conflicts of Interest

The author declares no conflicts of interest.

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# An introduction to little-known aspects of nonclinical regulatory writing

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## Abstract

Nonclinical evaluation is a key component of drug development. Traditionally, scientists have prepared much of the written regulatory documentation, with dedicated nonclinical writing being a niche profession. This is changing – the demand for nonclinical writers is growing due to the increasing complexity of drug development and regulatory requirements. Yet dedicated resources for nonclinical writers are scarce, and nonclinical health authority guidelines provide little guidance on regulatory writing. In this article, we present an overview of nonclinical development from the perspective of a regulatory writer, highlighting aspects that cannot be discerned from the guidelines. We then give an overview of nonclinical documentation and further describe the distinct challenges of nonclinical regulatory writing and how it differs from clinical regulatory writing. Finally, we discuss key attributes of nonclinical writers.



## Introduction

When considering drug development, people naturally think of human clinical trials. And when it comes to preclinical studies, many people assume that these are, as the name implies, conducted and completed before clinical trials are initiated (Figure 1). This reflects the common view that preclinical development is of little importance once human data have been obtained. Indeed, if you ask about the purpose of preclinical development, you will hear that it mostly consists of toxicology studies conducted to ensure a compound's safety before testing in humans.

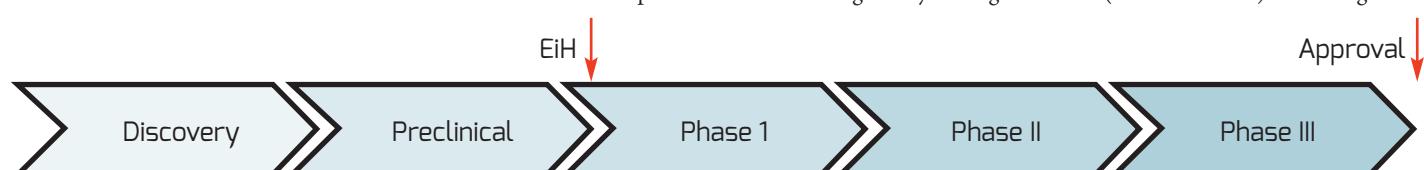
In this article we will challenge these views. We explain that preclinical evaluations comprise a comprehensive scientific programme that spans the whole lifecycle of the compound (Figure 2, Box 1). To underscore this, we use the term *nonclinical* throughout the article. We then discuss issues specific to nonclinical regulatory

documentation and key differences between nonclinical and clinical writing.

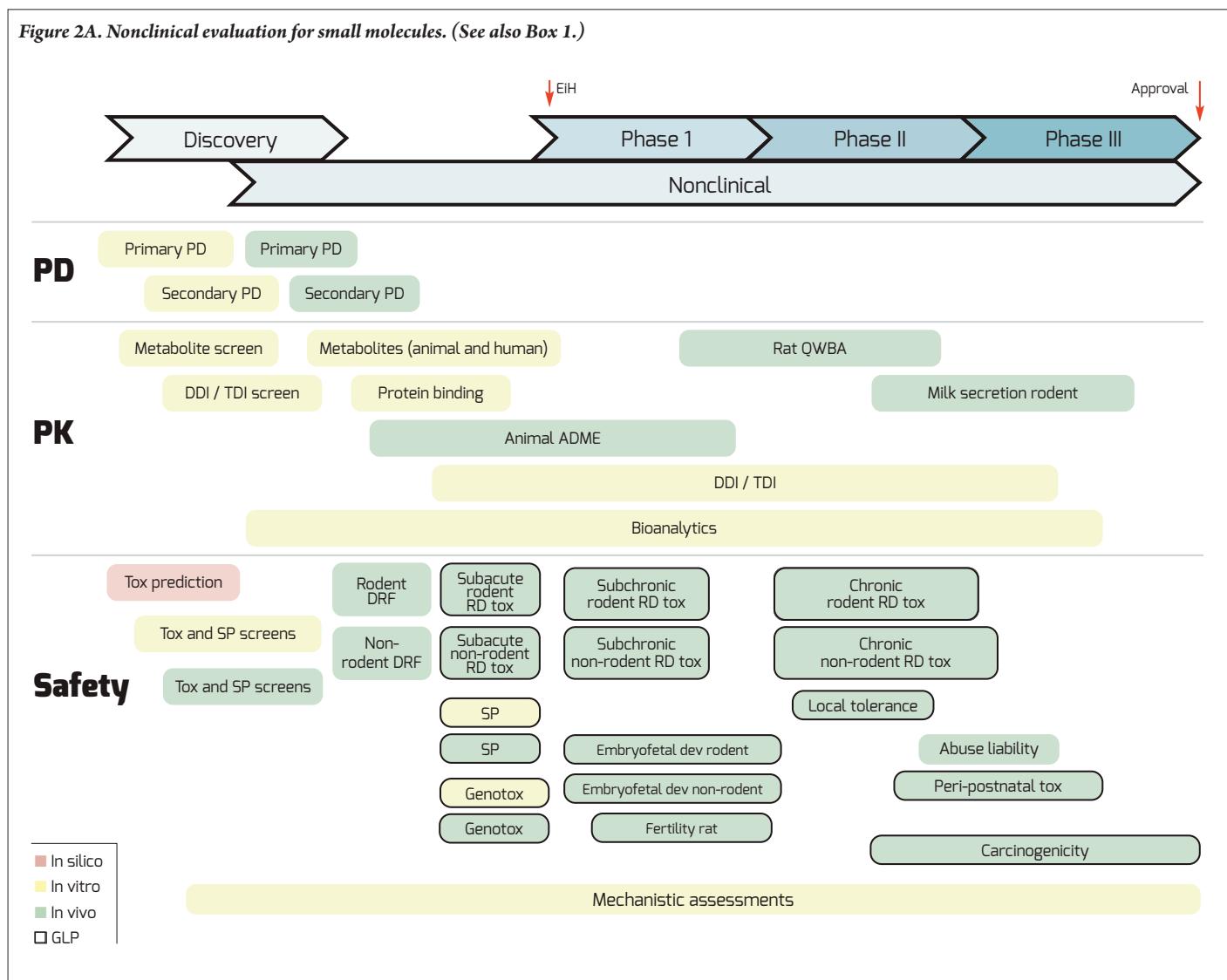
## The nonclinical regulatory framework and beyond

Nonclinical studies are required for the development of all new pharmaceutical compounds,<sup>1</sup> but the number and type of studies depend on the compound's characteristics, in particular whether it is a small molecule (Figure 2A) or a biologic (Figure 2B). For example, under certain circumstances, biologics are exempt from some pharmacokinetic and safety studies, although they often require additional case-by-case assessments.<sup>2–5</sup>

The regulatory requirements for nonclinical safety evaluation are outlined in the International Conference on Harmonisation (ICH) guideline M3.<sup>6,7</sup> Because this is a fairly broad document, it is supplemented by a large set of specialised guidelines (ICH S1A-S10) detailing the



**Figure 1. Conventional schema of drug discovery and development.** Traditionally, preclinical evaluations have been viewed as an intermediate and isolated step between drug discovery and clinical development (Phase I to III). EiH: entry in human.



**Box 1. Nonclinical evaluation for small molecules (Figure 2A) and biologics (Figure 2B).**

In practice, nonclinical studies start during the discovery phase and continue until (and sometimes beyond) approval. Nonclinical development covers a number of domains, from the biological research underpinning a compound's mode of action through its disposition in the body (pharmacokinetics) and safety assessment (toxicology).

(A) For small molecules, early studies, including in silico predictions and in vitro/in vivo screens, provide a valuable feedback for compound optimisation during the discovery phase. They also form the basis for managerial decisions to advance molecules into Good Laboratory Practice (GLP) safety assessments. GLP studies, if successful, enable the conduct of the first human trials. Larger scale and longer clinical trials in

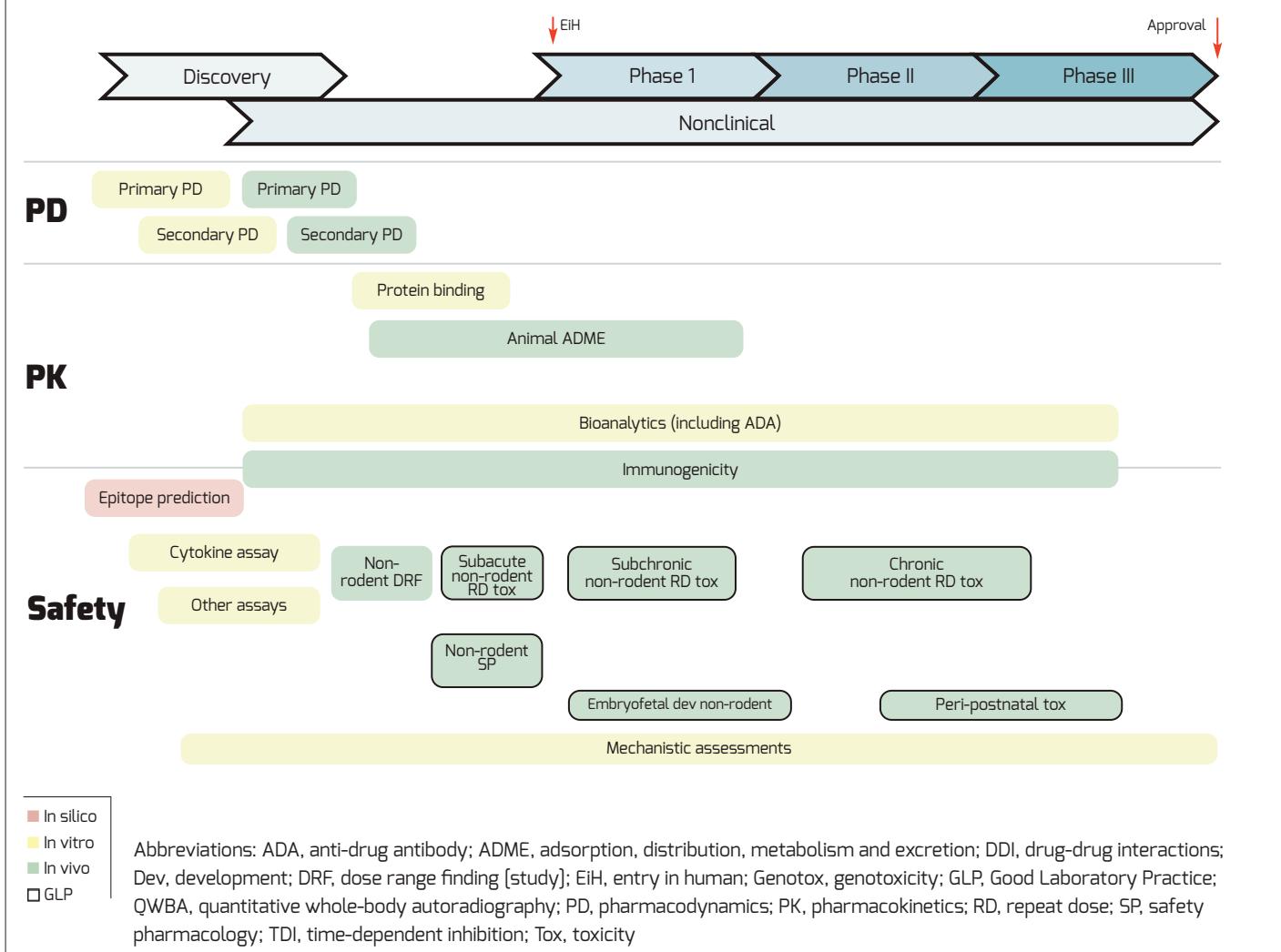
Phases II and III require more toxicological evidence, including longer (subchronic and chronic) repeated dose toxicity studies. Nonclinical studies required for marketing approval, such as carcinogenicity studies, should be initiated well in advance of the submission (usually during Phase III).

(B) For biologics, although nonclinical evaluation requires fewer studies, it may still become complex due to limited experience with new molecules and modes of action or to a lack of relevant species. In many cases, the only relevant species may be a non-rodent, and so rodent studies may be omitted. However, health authorities may also request that the non-rodent studies are supplemented with data generated in transgenic mouse models. Another challenge is immunogenicity, which

can lead to unwanted pharmacodynamic (lack of efficacy) or pharmacokinetic (high variability, fast clearance) effects or cause adverse reactions. Immunogenicity testing can therefore constitute a large portion of a nonclinical programme for biologics.

Of note, the figure only presents key nonclinical evaluations, which may consist of several separate studies. For example, carcinogenicity assessment typically consists of a 2-year rat study and a 6-month transgenic mouse study, both preceded by dose-range finding studies.

In general, the need for nonclinical studies should be assessed on a case-by-case basis; a real nonclinical programme is thus always tailored to the compound being developed.

**Figure 2B. Nonclinical evaluation biologics. (See also Box 1.)**

requirements for particular types of nonclinical studies or specifying programmes for certain compound classes or patient populations (Table 1). The guidelines for the first-in-human clinical trials provide additional details on the nonclinical programme, including more precise requirements for assessing pharmacodynamics<sup>8</sup> and determining the starting dose.<sup>8,9</sup> Nonclinical evaluation is further guided by a variety of cross-disciplinary documents.<sup>10</sup> For example, many nonclinical pharmacokinetic in vitro evaluations are mandated by drug-drug interaction guidelines.<sup>11,12</sup>

The methodology of nonclinical studies overlaps significantly with that of industrial toxicity testing. Hence, regulatory agencies expect Organisation for Economic Co-operation and Development (OECD) guidelines to be considered if applicable. These not only include

the well-known OECD GLP guideline,<sup>13</sup> which is the nonclinical sister to the Good Manufacturing and Good Clinical Practices, but also many internationally agreed-upon and validated toxicity testing methods.<sup>14</sup>

Although all of these guidelines are extensive and appear comprehensive, they cover, in fact, only a subset of the nonclinical studies included in submission packages. Additionally, they do not provide a general overview of how the nonclinical programme fits into the full drug development programme. To fill this gap, we address below four key points about nonclinical development.

#### Nonclinical studies vary greatly

Although nonclinical development is often associated with animal tests, like rat or monkey toxicity studies, in reality, the nonclinical

programme is much more diverse. Apart from in vivo toxicity studies, nonclinical investigations also include in silico, in vitro, and in vivo assessments of pharmacological effects and pharmacokinetic properties, as well as in silico and in vitro toxicity tests. Although safety testing must be conducted in two species (rodent and non-rodent), an overall nonclinical programme can involve more than two species because certain nonclinical questions may require special animal models. For example, our group has even worked on studies using woodchucks, one of the rare suitable animal models for hepatitis B. For biologics, the only relevant species may be a non-rodent, usually non-human primate, and thus the requirement for rodent studies can be waived. In addition to these in vitro and in vivo animal evaluations, many nonclinical in vitro tests are performed using human samples, such

as primary cell cultures or blood. Some nonclinical studies may be purely physico-chemical, for example, X-ray crystallography of a ligand-receptor complex.

Nonclinical programmes are also closely linked with medicinal chemistry and manufacturing. At the discovery stage, nonclinical data drive compound optimisation.<sup>15</sup> During nonclinical development, the formulation and even the molecular structure of the compound can change, necessitating bridging nonclinical studies. As manufacturing scales up, assessing impurities becomes an additional nonclinical issue.<sup>16</sup> For complex manufacturing processes, more genotoxicity testing may be needed than for the original active compound – we have seen as many as 30 studies for impurities.

Nonclinical methods are largely influenced by innovation. Pharmaceutical companies constantly seek to reduce both the attrition rate and the need for animal studies in nonclinical development by introducing new *in vitro* screening methods, such as human organs-on-a-chip.<sup>17</sup> Thus, novel methods are consistently being tested and presented to the appropriate regulatory bodies. The rise of biologics and other new types of pharmacological intervention<sup>18</sup> has

also prompted rethinking of the traditional approaches to nonclinical evaluation used for small molecules.<sup>3,4,19</sup> Following advances in understanding carcinogenicity and the increasing demand for early access to paediatric drugs, new ICH nonclinical safety guidelines (S1 and S11; see Table 1)<sup>20-22</sup> are in preparation.

In short, nonclinical studies vary greatly, and the nonclinical landscape continues to evolve.

#### **The nonclinical package includes early investigations**

Nonclinical evaluation lacks a definitive starting point, unlike the clinical programme, where first clinical trial approved marks the beginning of clinical development. The start of pivotal (GLP) toxicity studies is a significant milestone, yet it is preceded by many other investigations reaching back to the early discovery stage. These early studies are not specifically mandated by the guidelines but are driven by scientific and practical reasoning: No company would run an expensive GLP toxicity study without an extensive screening for possible toxicities, including *in silico*,<sup>23</sup> *in vitro*, and smaller-scale non-GLP *in vivo* investigations. Similarly, early assessment of pharmacokinetic properties informs both the

discovery programme (e.g., compound optimisation) and the design of the safety evaluations (e.g., safety-relevant human metabolites). If the compound progresses, almost all of these early studies will become part of the nonclinical package.

#### **Nonclinical studies continue after entry into human**

Although many nonclinical studies are completed before the first human clinical trials, nonclinical development continues far beyond. Some of these later studies are aimed at supporting late clinical phases (e.g., chronic repeated-dose toxicity studies), while others are required for marketing approval (e.g., carcinogenicity studies). Planning nonclinical studies to be run in parallel to clinical development is a challenge because nonclinical results must be delivered in time for applications for next clinical trials or marketing approval. In some situations, nonclinical studies may be conducted post-approval, either as part of post-approval commitments or to support post-marketing safety evaluation. Thus, nonclinical documentation support is usually needed throughout the whole lifecycle of the compound.



**Table 1. Key guidelines for nonclinical evaluation**

Guideline	Name	Description
ICH M3	Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals.	The key guideline, which describes the general principles, timing and standards for nonclinical safety evaluation.
ICH S1A	Guideline on the need for carcinogenicity studies of pharmaceuticals.	These three guidelines will be replaced by a single comprehensive guideline (ICH S1) on rodent carcinogenicity testing for human pharmaceuticals.
ICH S1B	Testing for carcinogenicity of pharmaceuticals.	
ICH S1C	Dose selection for carcinogenicity studies of pharmaceuticals.	
ICH S2	Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use.	The guideline describes the standard test battery for genotoxicity of small molecule compounds and provides recommendations for individual tests.
ICH S3A	Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies.	The guideline describes the assessment of systemic exposure in toxicity studies. It does not provide guidance for nonclinical pharmacokinetics and metabolism testing.
ICH S3B	Pharmacokinetics: Guidance for repeated dose tissue distribution studies.	Specific guideline for tissue distribution studies within the nonclinical pharmacokinetics programme.
ICH S4	Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing).	This small guideline sets out the minimal duration of chronic toxicity studies that is acceptable for submission (6 months for a rodent and 9 months for a non-rodent study).
ICH S5	Detection of toxicity to reproduction for medicinal products and toxicity to male fertility.	The key guideline for reproductive toxicity testing. It is currently under revision.
ICH S6	Preclinical safety evaluation of biotechnology-derived pharmaceuticals.	This guideline outlines the nonclinical safety evaluation for biologics. It is a supplement to ICH M3.
ICH S7A	Safety pharmacology studies for human pharmaceuticals.	The two guidelines provide recommendations for studies that examine unwanted pharmacological effects on physiological functions (so-called “safety pharmacology” studies). Safety pharmacology studies may be considered part of toxicological programme and summarised in the toxicology written summary.
ICH S7B	The non-clinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals.	
ICH S8	Immunotoxicity studies for human pharmaceuticals.	The guideline describes nonclinical testing for immunosuppression and immuno-enhancement. It does not cover allergenicity or drug-specific autoimmunity.
ICH S9	Nonclinical evaluation for anticancer pharmaceuticals.	The guideline describes specific requirements and certain toxicology study exemptions for nonclinical testing of anticancer compounds.
ICH S10	Photosafety evaluation of pharmaceuticals.	The guideline describes in detail phototoxicity testing of new compounds, excipients of dermal formulations and photodynamic therapy products and illustrates situations that do not require experimental evaluation in biological systems.
ICH S11	Nonclinical safety testing in support of development of pediatric medicines.	This will be a new guideline for nonclinical evaluation of compounds for paediatric use (“paediatric first” or “paediatric only”).
GLP	Good Laboratory Practice.	The quality standard for nonclinical studies. The OECD GLP is a common reference point, however, regional legal implementations can vary significantly. Studies conducted in a country that is not included in the OECD Mutual Acceptance Data system may be not accepted by some health authorities.
EMEA/ CHMP/ SWP/ 28367/07 Rev. 1	Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.	The cross-disciplinary guideline from EMA, which provides additional details for nonclinical programme intended to support entry in human.
ICH M7	Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.	A new cross-disciplinary guideline that complements the existing ICH Q3A and ICH Q3B guidelines. It contains considerations for the risk assessment for potentially mutagenic impurities.

**Note:** The EMA has a dedicated page containing a comprehensive list of nonclinical guidelines.<sup>10</sup>

### Nonclinical studies support labelling

For marketing approval submissions, nonclinical information is traditionally seen as corroborating clinical evidence. Safety assessments can provide mechanistic explanations of adverse reactions observed in humans, and pharmacokinetic evaluations can inform decisions on clinical pharmacology studies, but it is the clinical trial results that actually support labelling claims. However, some data cannot be intentionally obtained in clinical trials, most notably data on carcinogenicity and reproductive toxicity. Thus, labelling is directly influenced by the results of these nonclinical investigations, along with some nonclinical pharmacokinetic data (e.g., drug-drug interaction or transporter studies).

## Nonclinical regulatory documentation

Nonclinical regulatory documentation can be divided into three major domains:

- Summary documents for regulatory submissions
- Study reports with original data
- Various regulatory documents presented during the life cycle of a compound

The common documents with nonclinical content are summarized in Table 2.

### Summary documents for regulatory submissions

For clinical regulatory writers, the Investigator's Brochure (IB) is likely the most familiar document with nonclinical content. The IB contains a summary of all clinically relevant pharmaceutical, nonclinical and clinical data about a compound.<sup>24,25</sup> The IB is first prepared for the initial, first-in-human trial and is then updated at least annually and before any clinical trial application. The nonclinical section may be written by the scientists or by nonclinical writers. The first few versions are usually fairly extensive, but the section is usually condensed as clinical trials advance and clinical knowledge increases.

Along with the IB, the nonclinical Common Technical Document (CTD) Module 2 documents are the only nonclinical documents with clear guidance about their content (ICH M4S;<sup>26</sup> for more detail, see Debbie Jordan's overview of the CTD.<sup>27</sup>) These include three written summaries, for pharmacology, pharmacokinetics, and toxicology (sections 2.6.2, 2.6.4, and 2.6.6), which present an integrated summary of findings; three corresponding tabulated summaries (sections 2.6.3, 2.6.5, and 2.6.7),

which present the data in tabulated form with no interpretation; the nonclinical introduction (section 2.6.1), which contains a brief summary of pharmaceutical structure, pharmacological properties and intended clinical use; and the nonclinical overview (section 2.4), which provides an integrated assessment of the safety, pharmacokinetics, and pharmacology data in the context of the proposed clinical trial or label. Module 2 documents are submitted with marketing approval applications and with FDA Investigational New Drug applications (INDs), which are mandatory for initiating clinical trials in the US.<sup>28</sup> Similar, though less detailed, documents are required for clinical trial applications outside the US, such as the nonclinical sections of the Investigational Medicinal Product Dossier in Europe<sup>29, 30</sup> and Part 3 of the Australian Clinical Trial Exemption application.<sup>31</sup>

Importantly, the argumentation in the nonclinical documents changes as the compound advances in clinical development. Early submissions, such as FDA INDs, focus on non-clinical evidence for safety and pharmacological activity, including justification for the chosen nonclinical program and the adequacy of the safety precautions set in the clinical protocol. For marketing approvals, the writing task is different because nonclinical data must be discussed in the context of available human data with an emphasis on how they align with the effects observed in humans (e.g., pharmacological mechanism or adverse reactions) and labelling claims. The summary documents also become more extensive because the number of studies to include generally grows following the first-in-human trials.

A rarely discussed aspect of these submissions is the health authority responses and questions. Unsurprisingly, given their overall complexity, submissions do not elicit straight yes or no responses from the health authorities! Frequently, health authorities have questions about the submission data and their interpretation that must be answered within a limited timeframe – anywhere from one day to several months, depending on the country, submission, and number and type of questions. These may include, for instance, technical queries (e.g., a missing report signature), proposed alternative interpretations of findings, or requests for additional data to support a particular claim. These questions often require delving deeper into

the original study data or scientific literature and sometimes even planning a new study.

### Nonclinical study reports

Nonclinical study reports are included in CTD Module 4 of marketing approval applications and INDs. In Europe and other regions, a summary of the nonclinical findings is usually sufficient for a clinical trial application,<sup>29, 30</sup> but agencies may request study reports during the review. For a first-in-human clinical trial application, on average, 20 to 50 reports will be prepared, and even more reports are usually needed for a marketing approval submission. These reports, anywhere from 5 to 3,000 pages long, range from early pharmacology work to complex toxicity studies conducted under GLP. The reports may have been prepared in-house, at a contract research organisation, or even by another pharmaceutical company in the case of purchased compounds. Complex studies, most notably GLP general toxicity studies, include several substudies, so-called "phase" studies, which are ultimately incorporated into the final report. Coordinating the preparation and delivery of the phase reports can be complicated because they often come from different departments or contract research organisations. This can also be a challenge if submitting draft GLP toxicology reports to the FDA because they must contain a signed pathology phase report and must be followed within 120 days by the final report with a detailed list of changes.

In addition to the nonclinical studies, nonclinical writers support some studies in the clinical domain (CTD Module 5). These include in vitro and ex vivo pharmacokinetic evaluations with human biomaterials, as well as certain parts of clinical studies. Nonclinical writers also frequently support method validation and bioanalytical reports because analyses for both nonclinical and clinical studies are often performed by the same bioanalytical laboratory. Other examples include biomarker analysis and population pharmacokinetics studies, which are often conducted by nonclinical or cross-functional units.

There is a high turnover of nonclinical reports due to the relatively short duration and large number of studies. Reports are produced on an ongoing basis to inform regulatory and managerial decisions, with new findings sometimes leading to additional investigative studies. Writing activities must be coordinated

**Table 2. Common documents with nonclinical content**

Document	Nonclinical content	Content/Writing Guidelines	CTD Module	Submission package or Timepoint
Investigator's Brochure	This comprehensive document contains a summary of all clinically relevant pharmaceutical, nonclinical and clinical data about a compound.	ICH E6 <sup>24</sup>	Module 1 (IND)	Clinical trial application (CTA), IND
Investigational Medicinal Product Dossier	A high-level summary of the nonclinical programme. Usually, however, the dossier simply refers to the corresponding sections of the IB.	EU Guideline <sup>29</sup> EU Regulation <sup>30</sup>	–	CTA
Nonclinical Overview	The nonclinical overview provides an integrated analysis of the nonclinical programme, which includes justification for the nonclinical testing strategy and conclusions for the safety for the intended clinical trial or therapeutic use. Similar summary documents are submitted with clinical trial applications in some regions (e.g. in Australia).	ICH M4S <sup>26</sup>	Module 2, Section 2.4	IND, Marketing approval
Nonclinical Introduction	A small document (few pages) that contains a brief summary of pharmaceutical structure, pharmacological properties and intended clinical use of a compound.	ICH M4S <sup>26</sup>	Module 2, Section 2.6.1	IND, Marketing approval
Nonclinical Written Summaries	The documents contain high level summaries of pharmacology, pharmacokinetics and toxicology data, including a brief summary of the principal findings and a concise discussion and conclusion.	ICH M4S <sup>26</sup>	Module 2, Sections 2.6.2, 2.6.4, 2.6.6	IND, Marketing approval
Nonclinical Tabulated Summaries	The documents summarise pharmacology, pharmacokinetics and toxicology data in tabulated form with no interpretation. Similar tables are prepared for clinical trial applications in China.	ICH M4S <sup>26</sup>	Module 2, Sections 2.6.3, 2.6.5, 2.6.7	IND, Marketing approval
Nonclinical Study Reports	The reports are included in the CTD Module 4 of marketing approval applications and INDs. In Europe and other regions, a summary of the nonclinical findings is usually sufficient for a clinical trial application, however, all cited study reports must be available on request. Nonclinical regulatory writers can also support some reports included in the clinical CTD Module 5 (e.g., <i>in vitro</i> and <i>ex vivo</i> pharmacokinetic evaluations with human biomaterials).	No single guideline available, some scientific guidelines contain high level requirements for study reports.	Module 4, Module 5	CTA (on file), IND, Marketing approval
Briefing Packages	The briefing packages are the official way to request health authority feedback. They can be prepared by all departments – clinical, manufacturing, or nonclinical. Nonclinical background information and questions are commonly included in briefing packages for each department.	Agency-specific guidelines	–	Usually before next development step (e.g., before CTA, IND or filing)
Special Protocol Assessment	A special request for the FDA's feedback on the carcinogenicity study protocol. It contains the draft protocol, an integrated summary of nonclinical and clinical data, and justification for the selected doses and other critical design features.	FDA Guideline <sup>33</sup>	–	Usually when pivotal clinical trials commence
Paediatric Investigation Plan/Pediatric Study Plan	The plan contains a summary of nonclinical findings alongside with a summary of the nonclinical strategy to support paediatric use.	EMA Guideline <sup>34</sup> and template, FDA Guideline <sup>37</sup>	–	Before Phase II or pre-IND
Risk Management Plan	The plan contains a summary of safety-related findings.	EMA Guideline <sup>39</sup>	Module 1	Marketing approval (Europe and some other regions)
Regular reports	Safety findings are also reported as part of regular reports, such as DSURs, PSURs/PBRERs, orphan drug annual reports, and IND annual reports (these can be replaced by a DSUR).	ICH E2F, <sup>40</sup> ICH E2C, <sup>41</sup> and specific EMA and FDA guidelines and regulations	–	Usually annual submissions



between many different internal departments and contract research organisations. Companies establish their own procedures for preparing reports, starting with the fundamental question of whether to prepare complete regulatory reports routinely for all studies or only write the complete reports when necessary for submissions. The first approach may waste resources because many compounds do not proceed into clinical development. However, with the second approach, submissions can become extremely challenging because of tight timelines, which can be exacerbated by having to prepare many reports, sometimes for studies completed years ago.

To complicate matters further, nonclinical guidelines focus primarily on scientific methods and development strategy. In particular, the GLP and other guidelines provide only high-level requirements for study reports rather than detailed guidance on report structure. Unlike clinical reporting, which is guided by ICH E3, there is no single detailed reporting guideline for nonclinical reporting – not surprising given the variety of nonclinical studies. Overall, the quality and validation requirements for the studies and reports vary greatly, from strict GLP rules for pivotal safety evaluations to a more academic approach for pharmacology reports (some health authorities do not even require signatures for these). Hence, the internal reporting criteria must be set appropriately, but even when requirements for report content and formatting are set, many reports, especially for pharmacology, do not contain any standard text and must be written from scratch.

In addition to writing and editing documents,

keeping track of all the reports in the nonclinical package is an important activity for a nonclinical submission writer. This requires considerable attention because these reports build on each other to form the full picture of a compound's pharmacological, pharmacokinetic, and toxicological properties. The key difference between clinical and nonclinical regulatory writing is, however, the wider variety and greater quantity of nonclinical reports required during drug development.

#### **In-between activities and supporting documents**

Applications for clinical trials and marketing approval are the largest health authority submissions. Over the course of a compound's development, however, nonclinical writers will prepare many other regulatory documents.

Briefing packages, which most regulatory writers are familiar with, are the official way to request health authority feedback. They consist of up-to-date summary data on a compound, followed by specific questions, the sponsor's position on these questions, and supportive arguments. Briefing packages can be prepared by all departments – clinical, manufacturing, or nonclinical. Nonclinical background information and questions are commonly included in briefing packages for each department because clinical or manufacturing concerns may hinge on a nonclinical finding or study.

The Special Protocol Assessment (SPA) for carcinogenicity studies is a special request for the FDA's feedback on the study protocol. Classic rodent carcinogenicity studies take up two years of *in vivo* treatment (meaning up to 3 years from

start to final report) and cost up to \$4 million.<sup>32</sup> Given the uncertainty of a compound reaching the market, carcinogenicity studies are usually conducted during a late stage of clinical development, typically starting when pivotal clinical trials are initiated. The late start, cost, and length of these studies make them a risky undertaking. Recognising this, the FDA has included carcinogenicity protocols, along with stability protocols and pivotal clinical protocols, in its current SPA programme.<sup>33</sup> In addition to the draft protocol, the SPA request contains an integrated summary of nonclinical and clinical data and justification for the selected doses and other critical design features.

Additional documents that include non-clinical contributions are Paediatric Investigation Plans/Pediatric Study Plans<sup>34–37</sup> and Risk Managements Plans,<sup>38,39</sup> which require summaries of either overall nonclinical findings or safety-related findings. Safety findings are also reported to the various health authorities as part of regular reports, such as safety update reports (e.g., Drug Safety Update Reports, Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports for Medicinal Products),<sup>40,41</sup> orphan drug annual reports,<sup>42,43</sup> and IND annual reports.<sup>44</sup> The reporting requirements for these vary, but a compilation of either all nonclinical studies or all safety findings (including a literature search) during the reporting period is always expected.

#### **Nonclinical regulatory writers**

As described above, nonclinical regulatory documentation comprises a wide range of activities involving many different stakeholders. Thus, nonclinical and clinical regulatory writers require somewhat different skill sets.

Because of the many areas in which a compound must be tested nonclinically and the number of reports, nonclinical writers in pharmaceutical companies, unlike many clinical writers, do not specialise in a specific therapeutic or document category area. Nonclinical writers work closely with scientific experts across domains to prepare regulatory documents. Nonclinical development includes many specialised fields, so in some companies, the role of a nonclinical writer may consist of more editing than writing. In any case, a strong background in biological sciences, usually with some practical research experience, is necessary to understand the many *in vitro* and *in vivo* assays conducted.

As mentioned earlier, nonclinical development is a highly innovative field, with new technologies constantly being introduced, so a nonclinical writer needs to keep abreast of new scientific and technical advancements (see Box 2).

#### **Box 2. New FDA requirement for electronic submission of data for certain toxicology studies**

The managerial aspect of nonclinical submissions has recently become even more challenging due to a new FDA requirement for electronic data submission<sup>49</sup> coming into effect for certain toxicology studies (Standard for the Exchange of Nonclinical Data [SEND]),<sup>50</sup> a nonclinical variant of the Study Data Tabulation Model [SDTM]). Until now, raw study data have been archived and only submitted on request. This shift has led to an industry-wide scramble to prepare standardised study outputs and to reform processes to include these data files in FDA submissions.<sup>51</sup> Because the SEND data files are included in CTD Module 4, nonclinical writers involved in the assembly of nonclinical packages may find themselves coordinating both the preparation of study reports and the delivery of SEND files.

However, former scientists in a specific nonclinical domain, most often in toxicology, may switch to regulatory writing and thus provide specialised service in writing reports and summaries. In addition, some guidelines mandate that a scientific expert contribute to specific documents. For instance, GLP guidelines require an expert pathologist (often with veterinary qualifications) to write and sign the pathology study report, a critical component of in vivo toxicology study reports.<sup>45</sup>

Some scientists prepare reports and regulatory documents frequently, but others do so only rarely, so scientists often must be trained in report writing and the specific requirements of regulatory submissions documents, and especially in the differences with academic writing. However, scientists rely on nonclinical writers for more than preparing articulate and sound documentation; they also expect advice on regulatory matters, either by liaising with the regulatory lead or by providing information about best practices. Therefore, writers must keep up to date with official guidelines and continuously learn about best practices. For

example, interpretation of the GLP guidelines can differ between countries,<sup>46</sup> and studies conducted in a country that is not included in the OECD Mutual Acceptance Data system may be not accepted by some health authorities, such as in South Korea<sup>47</sup> and the UK,<sup>48</sup> which do not accept GLP studies conducted in China. Staying alert for such issues is another key part of a nonclinical writer's work.

Like other regulatory writers, nonclinical writers need to be skilled at managing projects and dossiers, communicating with and mediating between a variety of collaborators, understanding and following regulatory guidelines, and learning on the job. However, different from clinical writers, nonclinical writers must have a strong background in the biological sciences and must take a generalist approach to be able to cover the wide range of assays and topics included in nonclinical development.

#### **Conclusion**

Nonclinical evaluation is an essential and complex scientific programme that extends throughout a compound's full lifecycle and requires extensive regulatory documentation. Nonclinical regulatory writing has not been viewed as an integral part of nonclinical research until recently due to its high reliance on direct scientific input and wide range of assays. Scientists have been expected to both conduct studies and produce regulatory-compliant reports, so dedicated nonclinical writing has remained a niche profession. However, the increasing complexity of drug development, and, correspondingly, of regulatory requirements is leading to a growing need for expert nonclinical writing support and indeed the pharmaceutical industry is adapting to this. This increasing demand should continue in the years to come.

#### **Acknowledgements**

We would like to thank Dr Jacqueline Gillis, Dr Anke Luehe, and Mr Christopher Snyder for critically reviewing this article and providing helpful suggestions. We also thank Dr Luehe for providing figures that we used as a basis for the ones in this article.

#### **Conflicts of interest and disclaimers**

The authors are employed by F. Hoffmann-La Roche Ltd.

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# Reporting of preclinical research: What do we get told – when and how?

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## Abstract

At present, there are no specific requirements for the reporting of preclinical research, and many studies, particularly those with negative results, never get published. Despite the huge advances in communication opportunities, things have not really changed throughout the history of drug development. Sometimes researchers and scientists are hesitant to release results prematurely and there is a culture not to publish when studies have negative findings. However, routine and reliable reporting of all research – preclinical, clinical, laboratory, animal or human based, and with positive or negative outcomes – is essential to the future of collaborative and successful clinical research. There are several new ideas to promote this, and hopefully in years to come we will see all research results easily accessible and widely used.

## Introduction

The idea of “bench-to-bedside” clinical research has captured the interest of the medical world for some years now. Otherwise known as “translational research” or “translational medicine”, it encompasses all phases of clinical trials from the process of drug discovery and development in the laboratory, through to animal testing, human testing, and ultimately licensing, marketing, and commercial sales. The process can be lengthy and challenging; it is estimated that on average it takes 12 years for a drug to make it from the laboratory to routine use in patients and only 10% of drugs that start preclinical testing ever

make it to being tested in humans, let alone gaining a licence and making it into regular use.<sup>1</sup> Given this high attrition rate, how are the early phase results communicated to the scientific community? Is the current reporting culture appropriately presenting preclinical data so that the right novel molecules are pursued for the right reasons? Do the results reach the right people, such as key opinion leaders and disease experts, rather than get inappropriately emblazoned over the media or worse, lost to history, without being published at all?

How preclinical research gets published and advertised to the wider scientific community currently seems somewhat mysterious and ad hoc and despite guidelines from various sources, it is not necessarily reliable or reliably reported. Even the reporting of large-scale clinical trials involving thousands of patients are unreliably reported – estimates are that between 25% to 50% of clinical trials never have thorough results published. In light of this, it is perhaps unsurprising that small, laboratory-based research projects are even more erratically reported. The AllTrials campaign is fighting for all clinical trials to have their results published within two years of trial completion.<sup>2</sup> At present, this pertains only to clinical trials and not preclinical, but nevertheless is the start of an improved reporting culture.

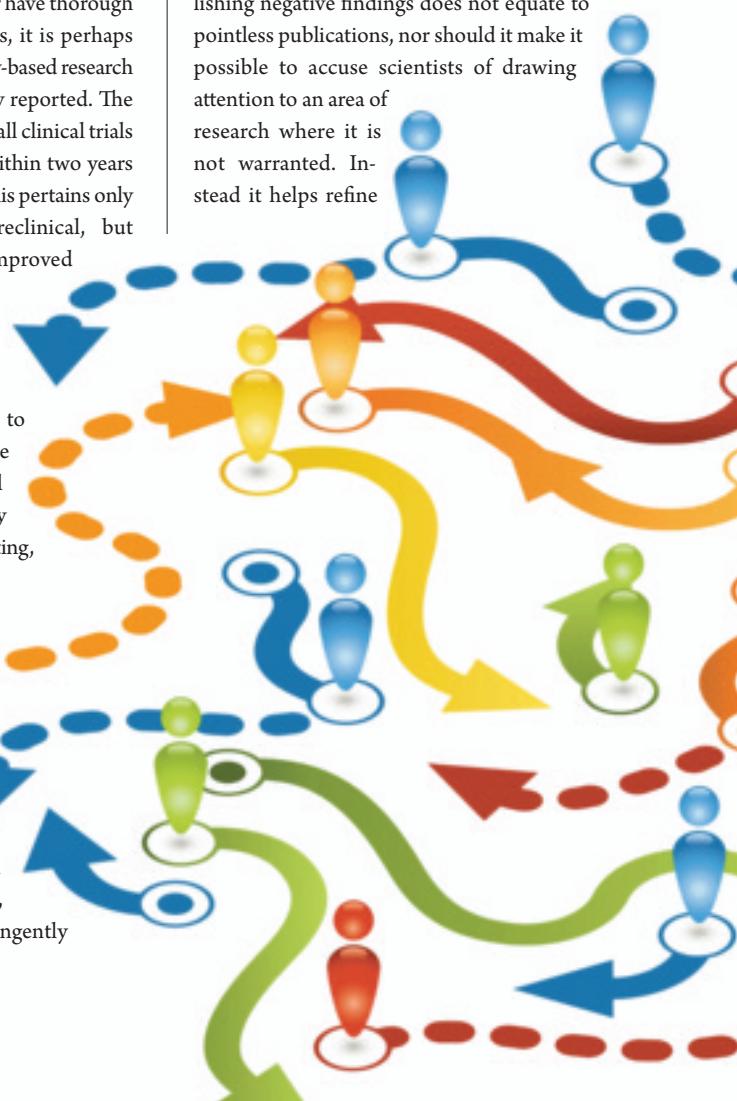
## Why are results not published?

The hesitations of scientists to publish results too early are understandable – often initial results suggest findings that may not be replicated upon further testing, and no reputable drug development team would wish to be accused of publishing misleading results.

However, preclinical research forms the basis of all subsequent drug development, and therefore needs to be as stringently

reviewed as Phase IV clinical trials that are about to present new medicines to the market. Early results can be reviewed by experts in the relevant field, which helps to decide which drug characteristics are desirable and worth further pursuit. The results can also be used to identify which drugs may have adverse effects or less desirable outcomes and can therefore be dismissed before further research replicated the same findings. Results ought to be published in a way that is understandable to the relevant reader and that can be subjected to valid critical appraisal.

There is a culture among all areas of science not to publish negative results – some high impact journals even state that “negative results are not accepted”. This attitude is clearly to the detriment of science and instils a philosophy that only positive outcomes are worthwhile – a very narrow-minded and restrictive stance.<sup>3</sup> Publishing negative findings does not equate to pointless publications, nor should it make it possible to accuse scientists of drawing attention to an area of research where it is not warranted. Instead it helps refine



the research process, preventing repetition of futile studies and cultivating a pro-active research community where lessons can be learned from one another and a more widespread collaborative attitude can be adopted.

## Initiatives in communicating results from preclinical research

The lack of reliable reporting of preclinical research is one that has been recognised already by the scientific community. In 2016, the commissioner of the FDA Rob Califf described an idea to develop a database of preclinical research where all research could be published and made widely available to the scientific community.<sup>4</sup> Such a database already exists for clinical trials – ClinicalTrials.gov.<sup>5</sup> In the United States it is a legal requirement for all Phase I onwards clinical trials to be registered on this site. It is an essential aspect of ethical and valuable clinical research. Such a resource for preclinical research would certainly help the reproducibility of results, prevent repetition of investigations that heeded negative results, and improve the transparency of the preclinical domain. Despite this, there was a general initial negative reaction from scientists, citing concerns that

such a requirement might restrict the innovative nature of preclinical and investigative studies and hinder those random and spontaneous discoveries that can sometimes lead to exciting findings.<sup>4</sup>

Almost certainly the benefits of such databases will eventually be realised and perhaps in the future they will be the norm, but at the moment the reporting of outcomes of preclinical and early phase clinical trials remains quite an ad hoc and mysterious activity. There are ample guidelines to aid researchers in how and what to report at all stages of clinical research. Those pertaining specifically to preclinical research include the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) of 2010 from the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3R),<sup>6</sup> which focus on research involving animals and set out guidelines for results reporting aiming to “maximise information published and minimise unnecessary studies”.<sup>6</sup> Furthermore, the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network provides more specific guidance for various types of preclinical research publication<sup>7</sup> and the Good Laboratory Practice regulations include study reporting.<sup>8</sup>

Another effort in recent years to improve the communication of preclinical and early phase clinical research to the wider scientific community is the introduction of several new journals and publications focusing on preclinical research and translational medicine. Such publications include *Translational Medicine Communications* and the *Journal of Translational Medicine*, both of which

provide a useful platform for wider distribution of preclinical findings and help lessen the difference between basic and clinical science.<sup>9</sup>

## The drug development process and why some “negative” discoveries can be worthwhile

Drug discovery and development are not a one-way path. Often, the first step is to identify a therapeutic target and to identify potential routes of modifying this. Sometimes the process starts the other way around, with a molecule being identified that has properties that may be of clinical benefit. The process then progresses to cell-based research in laboratories assessing the biochemical structures and properties of an agent, before progressing to animal studies, which form the basis for first-in-human clinical trials. At these stages safety, pharmacokinetic and pharmacodynamic data are established and the framework to subsequent phases of clinical trials are clarified. The whole process is fluid and dynamic and in the vast majority of cases, it is not a unidirectional and straightforward process, rather there are amendments and adaptations at each stage, making modifications along the way so that the process remains efficient and meaningful.

### Fluoxetine

An interesting example of a drug development process is fluoxetine, a drug now known for its antidepressant properties and widely used across the world. In the early 1970s Ely Lilly first investigated fluoxetine as an antihypertensive agent. It was found to have beneficial blood pressure lowering effects in animals, but when this reached human studies, such effects were not replicated. Instead of giving up on their new drug, an alternative use was sought. Fluoxetine was next considered as an anti-obesity agent, but again this did not produce promising results.<sup>10</sup> Eventually it found its place as an antidepressant – a transition aided by the discovery of the relevance of serotonin in the pathophysiology of depression (fluoxetine is a selective serotonin reuptake inhibitor), but also because of the increasing trend to recognise and diagnose mental health problems.<sup>10</sup> Even now fluoxetine (Prozac) has found its solid role in the pharmaceutical market. There are still research projects looking at its other potential therapeutic benefits outside its licensed uses (primarily major depressive disorder) and also investigating its adverse effects. A recent study by Hong and colleagues showed that chronic fluoxetine use in rats elevates blood pressure, heart rate, and



impaired cardiovascular reflexes.<sup>11</sup> Whether this will ever have clinical relevance or implication is uncertain, but it demonstrates the infinite research that drugs undergo.

### Aspirin

Another interesting example to consider is aspirin; a drug we all probably have taken at some point, indeed many of us take every single day – some for a headache or migraine, others to prevent cardiovascular disease, and many others for secondary prevention following a heart attack. It is probably one of the most familiar drugs to the general public – but what led to its development, what were people told initially, and why are its uses so diverse now?

The use of aspirin dates back to the time of the Egyptians, who noted the anti-inflammatory and analgesic properties of willow bark. Skip forward to the mid-1800s and the chemical in willow that is responsible for these useful effects is identified: salicylic acid. By 1876, the first clinical trial investigating aspirin as an antipyretic and analgesic agent took place. This trial identified several adverse effects of salicylic acid and the molecule had an acetyl group added to reduce its irritant effects.<sup>12</sup> Aspirin has been used as an analgesic agent ever since and, in 1950, it was the most sold painkiller. Interestingly, having been in commercial use for over one hundred years, it was only in the 1970s that its mechanism of action was discovered and from then on its uses have become increasingly diverse, with trials from the 1990s confirming its beneficial role in cardiovascular disease and making it the mainstay of treatment for this worldwide.<sup>12</sup>

The world was an interesting place in the years following the initial discovery of acetylsalicylic acid and because of this, some key facts about aspirin's development were not made evident in published data. It was being investigated in Germany throughout the 1930s and politics certainly had a significant impact on what the scientists behind aspirin felt comfortable to write. What does become apparent is that the acetyl molecule of salicylic acid was not the only chemical derivative to be investigated, but research actually started off with several other agents, each of which was dismissed for reasons that remain unclear. Indeed a few of these other agents had patents awarded to them, suggesting further investigation had been instigated, but the extent of this remains unclear to this day.<sup>13</sup> Without the publishing of preclinical research in

a routine and reliable manner, research findings can just disappear into history. No one other than the scientists involved can ever know what was discovered and the reasons behind certain drugs being pursued or dismissed. While in early 1900s Europe this patchy nature of research publishing is entirely understandable, in the world we live in today, where the wide sharing of information is so easy, it seems nonsensical that publishing can still be so ad hoc.

Despite aspirin's long history and known clinical benefits (as well as adverse effects – despite the adaptations made to the molecule, the limitations of aspirin use are well recognised), each year hundreds of new studies and trials are carried out, looking at aspirin's effects both in the lab and in man. There are trials registered looking at aspirin as an anticancer agent, for pre-eclampsia and only this week, there was a UK news headline claiming yet another new effect of aspirin. Research has recently shown that aspirin stimulates stem cells in teeth, enhancing tooth regeneration.<sup>14</sup> While this headline certainly draws in the reader and could indeed propose a novel use for aspirin in years to come, at present this really is just a laboratory-based finding and it will take years of further research to ascertain whether this effect can be replicated in human teeth and whether there is a viable administration method that would make this possible. The context of such results needs always to be considered – something that the media arguably are generally happy to ignore.

### Other implications in drug development

Drug repurposing (i.e., finding new uses for drugs that are already in use) is a substantial area of drug development and discovery. Both fluoxetine and aspirin demonstrate that when a molecule is discovered, even with a specific indication in mind, what it ends up being used for, or the specific adaptations that are needed to make it work effectively and safely in humans, cannot be predicted. This supports the fact the preclinical data should be circulated thoroughly, honestly, and in a manner that is easily accessible. There will likely be a far less questioning audience when there is clear evidence and explanation available

A challenge of publishing early phase and preclinical trial results is ensuring they are reported accurately and that results are relevant, realistic, and not misleading.

for why a drug has been repurposed or dismissed. As well as this, an outside party to the original research may have valuable contributions to make – perhaps even preventing the dismissal of an agent or identifying an alternate route to pursue.

### What should be published?

While referring to specific guidelines relevant to the particular nature and field of research, as a general rule there are several important areas that should be included in the report of a research project:

- The protocol or outline of study design, stipulating the specific aims of the study and how they will be achieved
- The raw data collected (as appropriate) and analysable data – raw data that has been extrapolated into a format so that statistical analysis can be performed. This is usually the most useful form of data to appear in a study report and forms the summary data that most readers will refer to for overall findings of the trial.<sup>15</sup>
- The data sharing plan – how the researchers intend to distribute their findings and at what point in the progress of their research they will do this<sup>15</sup>
- Statistical analysis methods – it is important for readers to know how the data was processed and tested in order for results to be replicated.<sup>15</sup>
- An overall study report summarising the key findings and next steps

This is merely a brief overview of the nature of preclinical reporting and individual adaptation and specific requirements for different publishers and publications.

### The future of preclinical research publication and what it means for medical communications

A challenge of publishing early phase and preclinical trial results is ensuring they are reported accurately and that results are relevant, realistic, and not misleading. Preclinical data may not ever be replicated in subsequent clinical trials, and even if positive findings are reproduced, it needs to be remembered that the sample groups



may not be representative of the whole population, or have some other confounding factor that restricts the more widespread impact. The outcomes of preclinical research need to be communicated appropriately so that key opinion leaders get interested and offer expert input, without releasing information too early that could be misleading and ultimately lead nowhere.

Medical communications professionals are key to the success of this. It is our role as experts in communication to help scientists present data, positive or negative, in a reliable, reproducible, and systematic manner so that it is widely understandable and its implications are made clear. Useful resources exist to aid with this and should be sought out when assisting with the publication of preclinical data. How the media choose to interpret such reports might be something we have less control over, but with clear, reliable, and transparent reporting, scientists and researchers can at least feel confident that the facts were published accurately.

## Conflicts of interest

The author declares no conflicts of interests.

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# Mind the gap – towards complete and transparent reporting of animal research

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## Abstract

Several initiatives have been taken to standardise the reporting of animal studies in peer-reviewed scientific journals, such as the ARRIVE (Animal Research: Reporting of In Vivo Experiments) and GSPC (Gold Standard Publication Checklist) guidelines. Surprisingly, many publications still lack key methodological details. As a result, animal studies are often criticised for poor scientific quality and low translatability to the clinic. To promote adherence to available guidelines, this article covers the rationales for including key parameters that are often overlooked, such as strain nomenclature, housing conditions, and behavioural test settings.

## Using rodents to understand human disease

On the journey from laboratory to clinic, animal testing provides the first opportunity to characterise the safety and efficacy of a drug candidate in a living organism. Depending on the disease target, the choice of species ranges from apes to zebrafish, with mice and rats making up about 95% of all research animals. Rodents are commonly used as disease models and are therefore inherently expected to be at least somewhat predictive for a human response to a drug. For model organisms to have this potential translational value, animal studies must be



designed, conducted, analysed, and reported with the highest scientific rigour. Regrettably, they still lag behind the standards for reporting human clinical data, although both share the common aim of generating unbiased data.

## Catching up with human standards

Reporting standards of human randomised controlled trials (RCTs) were improved by the introduction of the CONSORT (Consolidated Standards of Reporting Trials) statement in 1996.<sup>1</sup> Today, fundamental principles such as randomisation and blinding are regarded as the minimum requirements for performing and communicating science. Surprisingly, not all preclinical (and clinical) publications in peer-reviewed scientific journals seem to meet these very basic reporting standards. A 2009 survey by NC3Rs (National Centre for the Replacement, Refinement, and Reduction of Animals in Research) on the quality of reporting of publicly funded animal research in the UK and US revealed that over 85% of included publications lacked reporting of randomisation or blinding, and 41% lacked key information on

hypothesis and number/characteristics of animals.<sup>2</sup> In response to these survey results, NC3Rs developed the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines in 2010,<sup>3</sup> freely available at [www.nc3rs.org.uk/arrive-guidelines](http://www.nc3rs.org.uk/arrive-guidelines). They follow the example of the CONSORT statement and not only aim to improve the reporting of existing studies, but also the design of new animal experiments. The ARRIVE guidelines include a checklist of 20 items with descriptions of how to report a study comprehensively and transparently, e.g., by providing animal characteristics and statistical approach. Several other initiatives are dedicated to reducing the risk of bias in animal studies, such as CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) and SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation). The latter group also published SYRCLE's Risk of Bias Tool, an adapted version of the RCT-targeted Cochrane Risk of Bias Tool for animal studies,<sup>4</sup> and a Gold Standard Publication Checklist (GSPC),<sup>5</sup> which partially overlaps with the ARRIVE guidelines.

Despite such efforts to enhance the reproducibility of animal research, many publications still fail to provide even basic details on experimental design and analysis. As a result, they are rated as low-quality reports and are excluded from systematic reviews and meta-analyses. Such summaries of primary research articles represent the highest level of medical evidence and are used to guide clinical decision-making. Incomplete reports, even though the study may have been conducted perfectly, are therefore a source of bias and may lead to faulty conclusions about the safety and efficacy of a drug. Most professional medical writers and editors have extensive knowledge of the publication process and already have a good understanding of why details on blinding, randomisation, sample size, study objectives, or statistical analysis matter. For this reason, this article focuses on often under- or misreported methodological sections specific to animals, and the rationales for their importance.

## Species, strains, and why C57/BL6 mice do not exist

Most authors report the species and strain of the included animals, since these factors have long been known to affect behavioural and pharmacological responses. What is perhaps less known is that substrains of a strain, and even the same strain obtained from different vendors, may exhibit distinct phenotypes. For example, Wistar rats from Harlan Laboratories and Charles River vary in their response to the same acute myocardial infarction model, in that the former have a higher survival rate despite being more sensitive to cardiomyocyte damage.<sup>6</sup> Not only the vendor, but also the location of the vendor matters. Wistar rats from Harlan in the US (Hsd:WI) are behaviourally distinct from Wistar rats from Harlan in Europe (RccHan<sup>TM</sup>:WI).<sup>7</sup> Although both are of the Wistar strain, they originated from different institutes (Wistar Institute, Philadelphia, PA, US vs. Zentralinstitut für Versuchstierzucht, Hannover, Germany), emphasising the need for proper documentation of strain, substrain, vendor, and vendor location. This is further demonstrated by the widespread erroneous assumption that the correct nomenclature for the popular “Black 6” mouse strain is “C57/BL6”. As the original breeder, The

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Jackson Laboratory, put it in its blog post: “There is no such thing as a C57/BL6 mouse!” Instead, there are two distinct breeding colonies denoted as C57BL/6J (“J” for Jackson Laboratory) and C57BL/6N (“N” for National Institutes of Health), from which many substrains have emerged, such as C57BL/6NCrl (Charles River) and C57BL/ 6Jcl (Clea Japan).

Genetic and phenotypic differences both within and among populations are well established, so authors should always include the complete substrain designation indicating the laboratory maintaining the colony. For genetically modified animals (e.g. knockout or transgenic), additional information is needed. Guidelines and a checklist for reports on mutant studies have been provided by Crusio et al.<sup>8</sup>

Failure to mention sex and age may result in skewed data interpretation, as these factors are known to affect pharmacokinetics and pharmacodynamics in humans and laboratory animals. Fortunately, reporting percentages have markedly increased in the last two decades; nevertheless, a study found that still only 50% of the included articles published in 2014 reported both sex and age of their mice.<sup>9</sup> There is hardly an excuse for not including these variables, since they are available to all researchers and do not take up much space. Simply providing the weight or the developmental stage of the animals (e.g. “juvenile” or “adult”) instead of their age does not suffice, since these vary greatly across laboratories. According to a survey by Jackson et al.,<sup>10</sup> the age at which rodents are considered “adult” spans from 6 to 20 weeks (mice) and 8 to 16 weeks (rats). Since these ranges encompass distinct developmental events, they should be replaced by the actual age (mean or median age, variation, and age range). Moreover, weight and health/immune status of all included animals are needed.

## To enrich or not to enrich?

Laboratory housing conditions significantly influence behaviour and pharmacological response, and should be reported in detail. Since mice and rats are very social animals, isolating them may induce stress and interfere with the effects of a drug. Distinguishing between single- and group-housed animals is therefore important. Perhaps less known, mice and rats are sensitive to environmental complexity. In the 1940s, the influential psychologist and neuroscientist Donald Hebb took some laboratory rats home for his children to play with. Surprisingly to him, these animals subsequently performed better on cognitive tests than animals housed only in the laboratory. In the following decades, it was found that animals in enriched cages (containing sensory stimulation such as nesting material, tunnels, cardboard boxes, or chewing toys) but not control cages had more synapses, more and longer dendrites, and were protected against several types of brain injuries. Given these marked structural brain changes, care should be taken to adequately report the presence or lack of any cage enrichment for laboratory animals. Authors should refrain from referring to “standard cages” without further clarification, since the standard in one lab may be a cage with bedding only, while in another it may also contain shelter and toys. Publication writers should therefore clearly specify the number of animals (and sex thereof) per cage, model and size of cage and lid, presence and type of any enrichment, and frequency of cage change. Moreover, they need to describe the temperature and lighting in the room as well as the nutrition type and feeding regimen. For a comprehensive guide on the animal housing description, I recommend the aforementioned GSPC guidelines provided by SYRCLE.<sup>5</sup>

## Reporting behavioural tests

Although animal behaviour is central to evaluating drug efficacy, publications frequently lack a detailed description of performed tests. Comprehensive guidelines on the correct reporting of preclinical behavioural testing seem to be absent: The ARRIVE guidelines only devote two



lines to this effect, in which they prompt the author to clearly define the experimental outcome (i.e. behavioural change). GSPC guidelines also lack a complete list, although they at least regard the frequency of handling as a relevant variable. Given the multitude and complexity of available behavioural tests, a concise checklist is no easy task.

However, some general considerations apply to most behavioural tests and should be reported in all behavioural publications to facilitate scientific transparency and unbiased data interpretation. The most obvious consideration is the precise description of the behavioural test. For example, the Novel Object Recognition test, a popular cognition test in rodents, consists of multiple steps: habituation, training, and testing. The total test duration is 1 to 4 days, depending on the length of the habituation of the animal to the arena. Several lengths have been reported across laboratories, spanning from 2 minutes to as much as 2 hours. As long as the durations of each phase and the intervals between them are reported, this is not a major source of concern. However, it becomes a problem when authors deviate from the original protocol without mentioning their modifications; or worse, when they only provide the name of the test. In all tests comprising multiple phases, all durations and intervals in between should be given, along with any time allowed for acclimatisation to the behavioural rooms immediately prior to testing. The general rule of thumb here is to provide as many details as possible: If water is involved (e.g. Morris Water Maze or Forced Swim Test), provide the temperature and frequency of changing; if an apparatus is used, always report the size and material, as these can affect the response to a drug agent.

From a human perspective, it is easy to imagine that we probably perform better at a cognition test during the day than in the middle of the night. The same has been observed in (nocturnal) rodents – the time of testing (active vs. inactive phase) significantly affects their behaviour. Testing

### Failure to mention sex and age may result in skewed data interpretation, as these factors are known to affect pharmacokinetics and pharmacodynamics in humans and laboratory animals.

should therefore preferably be conducted in the dark (active) phase, unless it is known that a particular measure is not impacted by circadian rhythm. This does not only apply to behaviour, but also to the collection of any tissue that is sensitive to the photoperiod. In addition to information on the light cycle in the animal room, publications should

therefore include the time of the

day in which behavioural data or tissue were collected, as well as the light intensity (in lux) where applicable. Authors should also state if all tests were conducted by the same experimenter and how often the rats were handled prior to testing. Moreover, if more than one test was used, the number of days in between tests and the order of the tests should be reported, especially if one of them is stressful for the animals. Timelines of experimental events are a good way to graphically represent complex designs or testing batteries.

### Drug intervention and tissue collection

Any drug treatment must be clearly described, including the dose per weight, volume of injection, route of administration, frequency (including the time of the day it was given), exact vehicle, and method of preparation (e.g. sonication, multiple dilutions, etc.). Moreover, the euthanisation process and tissue collection must be documented, such as euthanisation method, time of day, whether all animals were euthanised on the same day, if randomisation was applied, and how tissue was collected. Instead of simply writing “liver tissue was obtained”, it should be mentioned which lobe the tissue was

taken from and how it was stored during and after the collection process. This might be obvious to many, but papers frequently lack basic information on tissue processing, e.g. dissection method, centrifugation speed, or freezer temperature. If decapitation is used, include measures of how rodents were protected from the smell of blood to prevent any confounding hormonal effects (e.g., they might have been housed in an adjacent room and brought into the decapitation room by an experimenter free of blood scent).

### How can we improve reporting standards?

By including or omitting methodological details, authors tremendously influence the quality of the article and the ability to draw meaningful conclusions from the results. With the omission of important details, readers are left to assume the worst-case scenario – that they have not been considered or performed. As a consequence, the overall relevance and quality of the data might be assessed as poor whether it is or is not. Unless research is adequately reported, the time, effort, and resources invested are wasted. In the case of preclinical studies, wasted resources may mean unnecessary loss of animal lives, which should be prevented at all costs. It is therefore the responsibility of the author to adhere to current guidelines such as ARRIVE or GSPC to reduce the risk of bias and maintain a high scientific standard in preclinical research. Journals need to implement adherence to these guidelines (e.g., by requesting a filled-out checklist at submission) rather than just endorsing them passively. They also need to provide authors with sufficient space to include all relevant details, either in the manuscript body or in supplementary files. New medical writers and researchers could greatly benefit from education and training opportunities that address the issues mentioned in this article in greater detail. Transparency

may also be increased by animal registries such as [www.preclinicaltrials.eu](http://www.preclinicaltrials.eu), in which researchers pre-register details of their experiment in an online database like [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for human trials.

This would allow medical writers to refer to the registry and select the key information relevant to the article at hand, which may improve the quality of future reports and contribute to less



bias. Ultimately, the value and clinical meaningfulness of animal studies hinges on the thorough reporting of experimental methods. Authors and medical writers involved in the publication process should therefore be aware of the importance of including even seemingly small details, as these may alter the reproducibility and generalisability of the study outcomes.

## Acknowledgements

Special thanks to Denise Happ for her excellent comments on this article.

## Conflicts of interest

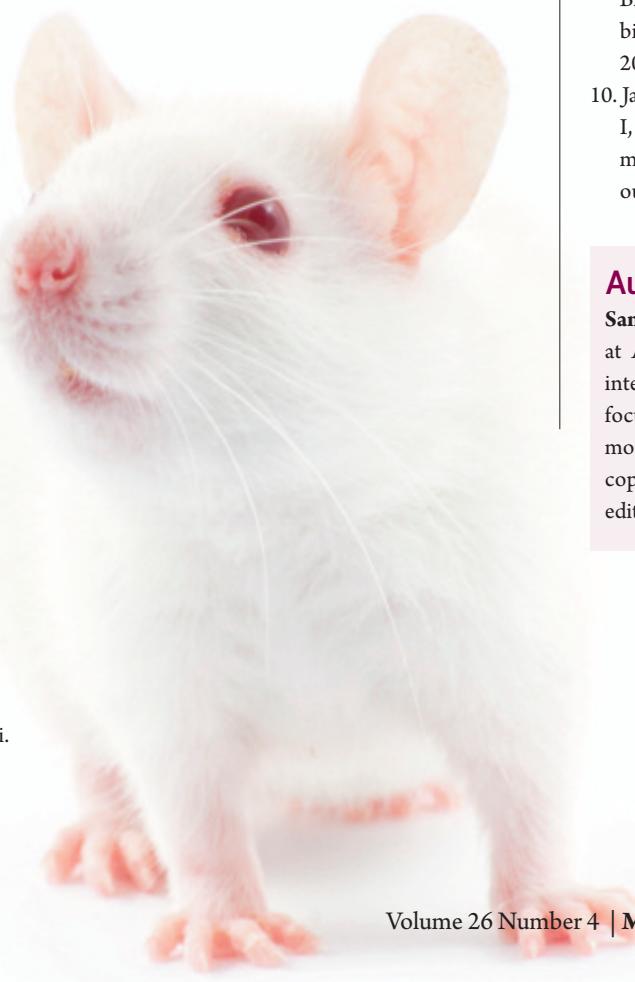
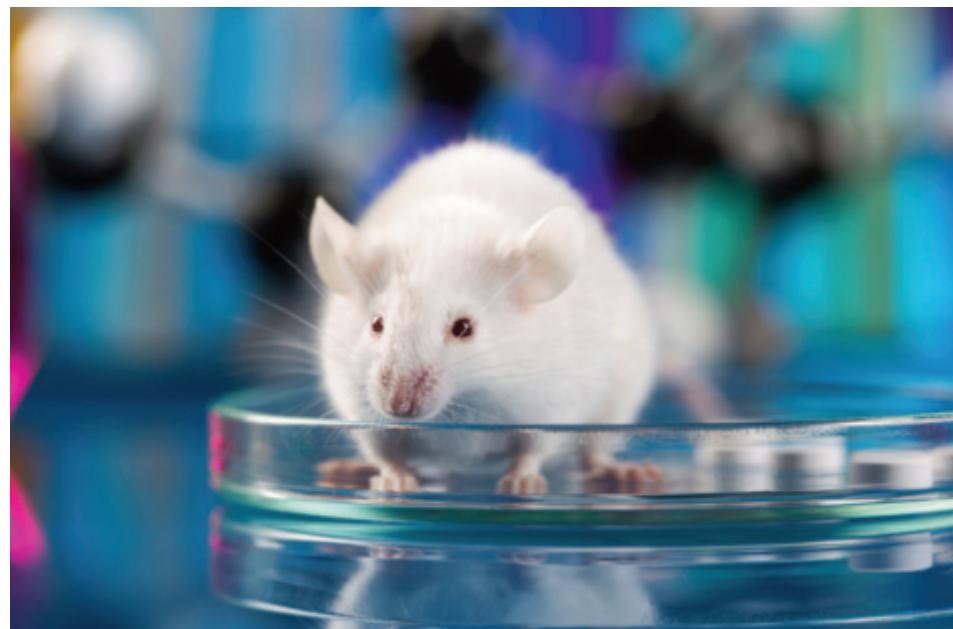
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# The reproducibility crisis in preclinical research – lessons to learn from clinical research

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## Abstract

In recent years, the robustness and reproducibility of preclinical data have been a topic for discussion. Quality standards and good practices are often not well defined for different *in vitro* methods and *in vivo* models, and not harmonised amongst preclinical research laboratories. This results in poorly reliable literature, has a negative impact on the bench-to-bedside time for new drugs, and increases the resources needed for clinical development. Clinical research, on the other hand, is tightly regulated and has high quality standards in place. Although improvements are slowly introduced, preclinical development (especially in its confirmatory phases) would benefit from taking a closer look and adapting more of the internationally accepted principles used in clinical research.

Reproducibility issues are gaining awareness amongst preclinical scientists: in a *Nature* survey, 52% of researchers state that there is a significant

crisis.<sup>1</sup> The published literature is a common source for potential new drug targets used by the pharmaceutical industry, and publication results are routinely validated in-house to ensure reproducibility. According to Prinz et al., almost two-thirds of the validation projects conducted at Bayer from 2007 to 2010 showed inconsistencies in results (including some from prestigious journals).<sup>2</sup> Begley and Ellis reported that researchers at Amgen could only confirm the scientific findings of six out of 53 (11%) landmark studies.<sup>3</sup> In addition, more than 70% of the researchers who participated in the *Nature* survey have failed to reproduce another scientist's results, and more than 50% admitted to having failed to reproduce their own.<sup>1</sup>

The reproducibility crisis is a quantifiable economic problem. Venture capital firms consider that, when repeated by an independent laboratory, the experiments in at least 50% of published studies do not provide the same results.<sup>4</sup> In the US alone, US \$28 billion per year are spent on preclinical research that is not reproducible.<sup>5</sup> More importantly, the lack of reproducibility has a negative impact on the bench-to-bedside time for new medicines, and increases drug development costs, as each study replication conducted by the pharmaceutical industry to validate academic research findings requires 3 to 24 months of work and US \$500,000 to \$2 million.<sup>5</sup>

Data robustness becomes even more important at later stages of preclinical research, when results determine "go/no-go" decisions for drug candidates to enter clinical testing. A meta-analysis identified higher effect sizes in animal models of stroke in studies with low quality standards.<sup>6</sup> This implies how low quality research standards can make drug candidates look more promising than they actually are.

## What is behind the reproducibility crisis?

Participants in the *Nature* survey consider that the main reasons are pressure to publish and selective reporting.<sup>1</sup> For academics, publishing is a career essential (e.g., for research funding, job

promotion, or tenure). Journal editors, referees, and grant reviewers look for the perfect story: simple, clear, and complete.<sup>3</sup> These demands tempt investigators to cherry pick experiments for publishing, develop hypotheses to fit the data, or keep collecting data until the desired significance level is reached (p-hacking). Competition among laboratories and pressure to publish among scientists may result in negligent controlling or reporting of experimental conditions.<sup>2</sup> Another issue is the bias towards publishing positive results and the difficulties in publishing results that contradict data in high-impact journals or currently established opinion (publication bias).<sup>2</sup> This leads to strengthening certain hypotheses, even if there is a body of unpublished evidence against them.

Published preclinical research often lacks proper quality standards in study design (e.g., blinding and randomisation) and validation

of research tools that ensure the data obtained is meaningful and unbiased. Begley and Ellis observed that authors of reproducible preclinical cancer studies had paid close attention to controls, reagents, and description of the complete dataset, while in studies that could not be reproduced, data were not routinely analysed by blinded investigators and often results from only one experiment were presented.<sup>3</sup> According to Freedman et al., errors leading to irreproducibility of preclinical data can be due to study design, biological reagents and reference materials, laboratory protocols, and data analysis and reporting.<sup>5</sup>

An enduring challenge in drug development is the erroneous use and misinterpretation of preclinical data from cell lines and animal models. *In vitro* cell culture systems are crucial research tools for analysing complex mechanisms regulating cell biology. However, over 480 misidentified cell lines (as of November 2017) routinely used in published studies are

Low quality standards can make drug candidates look more promising than they actually are.



contaminated, very frequently with HeLa cells (list available from the International Cell Line Authentication Committee [ICLAC]).<sup>7</sup>

The causes behind the reproducibility crisis are not limited to a specific field (in vitro or in vivo) of preclinical research or therapeutic area. The limitations of preclinical cancer models include (i) the use of a small number of poorly characterised tumour cell lines that inadequately recapitulate human disease, (ii) the inability to capture the human tumour environment, (iii) the lack of consideration for pharmacodynamics and pharmacokinetics, (iv) the use of problematic endpoints and testing strategies, and (v) the regular exclusion of predictive biomarkers for efficacy.<sup>3</sup> In the amyotrophic lateral sclerosis (ALS) field, Steve Perrin and his team re-examined 100 compounds that had been

identified as candidates for therapy in an ALS mouse model.<sup>8</sup> Most of these compounds failed to slow the disease in animals (including eight drugs that had previously looked promising, proceeded to clinical trials, and ultimately failed). These discrepancies are likely due to the low quality standards of the original publications, as most did not include statistical models to minimise experimental noise or implement blinding and randomisation procedures.

### What is the current situation and what could be done?

There are no commonly accepted and followed guidelines and quality standards for

The preclinical research outside those intended for studies that directly support drug marketing authorisations.<sup>9–12</sup> Indeed, none of

reproducibility crisis is a quantifiable economic problem.

the existing GxP standards (Good Laboratory Practice [GLP], Good Clinical Practice [GCP], Good Manufacturing Practice [GMP], etc.) can be used to ensure high quality preclinical research outcomes. Whether conducted in an academic or industrial laboratory, this non-regulated research is, however, essential to identify and validate novel drug targets and to build the basis for successful translation of preclinical data into clinically meaningful efficacy. Thus, there is a need for new specialised Good Research Practice (GRP) guidelines that focus on study design, unbiased conduct, statistical analysis, and transparent reporting.

Clinical research, on the other hand, is highly regulated and adherence to quality standards is routinely monitored. Human experimentation has strong ethical restrictions that require researchers to comply with higher research standards to avoid submitting study participants to unnecessary risks. There are several lessons that preclinical research could learn from clinical research regarding quality standards.

### Lessons to learn from clinical research

Clinical research is not perfect: A recent analysis of more than 5,000 papers in eight leading medical journals showed that roughly 2% of randomised controlled clinical trials may include fabricated data or lack adequate ethical approval.<sup>13</sup> However, clinical research is supported by strong standards and well-established procedures, as the following examples demonstrate, which could be used in preclinical research.

#### Declaration of Helsinki

As the cornerstone document of clinical research ethics, the Declaration of Helsinki helps ensure that the risk to trial subjects is proportionate to the benefit expected to society. Similar codes of practice would help preclinical researchers to realise that there is an implicit responsibility in all their activities. Currently, a similar concept exists only for animal research: the 3Rs (Replacement, Reduction, and Refinement) are considered in the US Guide for the Care and Use of Laboratory Animals and the European Directive 2010/63/EU.<sup>14,15</sup> These guidelines encourage finding alternatives to the use of animals, using the right number of animals, refining breeding, accommodation and care, and minimising distress. Of note, “reduction” means using the minimum number of animals required

to obtain statistically significant results based on power calculations (and not less than those); the same principle is applied for sample size calculations in clinical trials.

#### ICH E6 (GCP)

The International Conference for Harmonisation (ICH) guideline E6 covers ethical and scientific quality standards for designing, conducting, recording, and reporting clinical trials, and enhances data credibility. Amongst other, ICH E6 includes the following concepts:

- The Independent Ethics Committee (IEC) or Institutional Review Board (IRB) are independent bodies constituted of medical, scientific, and non-scientific members who ensure protection of the rights, safety, and well-being of the participants of a clinical trial by reviewing and approving essential trial aspects such as the protocol and its amendments, or the suitability of investigators and facilities. The Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)<sup>16</sup> and the International Council for Laboratory Animal Science (ICLAS)<sup>17</sup> carry out a similar function in animal experimentation: promoting proper treatment and ethical use of animals in science. Other areas of preclinical research, such as cell line or in vitro work, still lack a mechanism to obtain feedback on quality and relevance.
- Adequate and accurate source documents and trial records must be maintained. Source data should be Attributable, Legible, Contemporaneous, Original, and Accurate (ALCOA principles to ensure data integrity), as well as complete. Furthermore, any changes to source data should be traceable and not obscure the original entry (i.e., audit trail should be maintained). In preclinical research, there is still no clear consensus on which is the full set of essential parameters to be recorded in a specific experiment. Furthermore, the use of lab notebooks as tools to record research results is not standardised, and practices such as data witnessing are often not implemented.
- GCP states that qualified individuals should be involved in the conduct of a trial. Frequently, errors in preclinical research result from the incorrect analysis of data, suggesting

#### There are several lessons that preclinical research could learn from clinical research regarding quality standards.

biostatisticians to have a more relevant position in the experimental planning and analysis of preclinical data. In addition, medical writers as specialists in guidelines and good reporting practices have become essential in clinical research, and could equally contribute to enhance quality standards in preclinical research reporting.

- Audits serve to evaluate trial conduct and compliance with the protocol, standard operating procedures (SOPs), GCP, and regulatory requirements. In non-regulated preclinical research, monitoring of compliance with quality requirements that ensure unbiased conduct of research is increasingly becoming the focus of discussion, and has already been performed at contract research organisations (CROs) offering preclinical services. Furthermore, these routine audits could be interesting for agencies funding preclinical research.

As mentioned, preclinical research studies intended to support drug marketing applications are governed by strict regulations set by GxP.<sup>9-12</sup> However, these standards are not suitable for non-regulated, preclinical biomedical research and there is a need for the specialised set of GRP guidelines already discussed. Regarding *in vitro* cell culture, Good Cell Culture Practice (GCCP) (principles for standardisation, rationalisation, and international harmonisation of cell and tissue culture laboratory practices) has already been defined.<sup>18</sup> Nevertheless, consensus procedures for unambiguous authentication and identification of cell lines are still missing, and cell line misidentification, contamination, and genotypic and phenotypic instability remain issues.

#### ICH E8 and ICH E9

The ICH E8 guideline (“General Considerations for Clinical Trials”) provides recommendations for the design, methodology, and analysis of clinical trials, and ICH E9 (“Statistical Principles for Clinical Trials”) attempts to harmonise the principles of statistical methodology applied to them. Recently, international research consortia started to conduct so-called preclinical Phase III trials (i.e., multicentre, randomised, blinded animal studies) to test drug efficacy. These preclinical trials allow larger sample sizes and reduce bias, thus improving robustness and

translational predictability. They also address the reaction norm issue (whether response of an organism to an experimental treatment can be affected by environmental factors such as food and housing conditions).<sup>19</sup> Trials combining data from different centres with slightly different environmental conditions are well suited to analyse the robustness of effects and the reproducibility of *in vivo* experiments.

#### Transparency

The EMA Policy 70 is an attempt to enhance transparency by publishing clinical data for medicines once the decision making process on an application for an EU-wide marketing authorisation is complete.<sup>20</sup> This implies having open access to full datasets from those trials. In similar ways, some journals publishing biomedical preclinical research have now implemented “open data” policies: publications need to include full datasets, biological properties of all samples, and complete methodology. The Transparency and Openness Promotion (TOP) guidelines advise journals and funding agencies on how to incentivise transparency in planning and reporting preclinical research.<sup>21</sup>

#### Registration of clinical trials

Clinical trials need to be registered, as this avoids reporting bias, a common problem in preclinical research.<sup>22</sup> Notably, an increasing number of journals in preclinical research now offer the “Registered Reports” publishing format, in which peer review is conducted prior to data collection, based on the importance of the research question and the quality of the methodology. Article acceptance for publication is ensured unless quality assurance or unresolvable reporting problems arise.

#### Reporting guidelines

Many journals require that authors follow the Consolidated Standards of Reporting Trials (CONSORT) statement, an evidence-based, minimum set of recommendations for complete and transparent reporting of randomised controlled trials.<sup>23</sup> Several reporting guidelines have been developed for preclinical research, including National Institutes of Health’s (NIH) Principles and Guidelines for Reporting Preclinical Research, Nature’s checklist, the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines,<sup>24</sup> and the Cell Press’s Structured Transparent Accessible

Reporting (STAR) Methods.<sup>25</sup> They are intended to prompt authors to disclose technical and statistical information and reviewers to consider relevant aspects for research reproducibility. However, the huge variability of experimental designs and analytical techniques needs to be accounted for. The community-driven approach to this situation was the definition of “minimum information” checklists. The Minimum Information About a Microarray Experiment (MIAME), developed in 2001, was the first of such guidelines, and details which information needs to be provided to ensure reproducibility and unambiguous interpretation of microarray-based data.<sup>26</sup> Similar guidelines for other preclinical research techniques are described at the Minimum Information about Biological and Biomedical Investigations (MIBBI) portal, although only a few methods are covered so far.<sup>27</sup>

### A word of caution

Clinical and preclinical research are not directly comparable. In basic and preclinical research, scientists require enough freedom to use their creativity, which is key to the advancement of science and thus the development of novel drug candidates and innovative medicines. However, science progresses by building on existing knowledge, making rigorous, reproducible, high quality studies crucial.

The importance of finding a compromise between the need to trust conclusions of published research findings and the freedom for scientists to explore and innovate, has led to the concept of exploratory and confirmatory preclinical studies: at the exploratory stage, statistical testing and low quality standards should be acceptable as long as the experimental procedure is transparently described. However, for confirmatory studies (aimed to demonstrate robust and reproducible treatment effects), proper study design and implementation of the highest quality standards are essential, even if time- and resource-consuming.<sup>28</sup> Preclinical studies supporting decision making processes (e.g., whether to advance to animal studies or to first-in-human trials) should, therefore, be designed and treated as carefully as any clinical trial.

### Conclusion

Some of the concepts from clinical research are already starting to be applied in the preclinical



setting, and various approaches to enhance the robustness of preclinical data are being considered (strict adherence to quality standards, multicentre collaborations, data sharing, etc.). It seems worth noting that clinical research has gone a long way to improve its quality standards. These developments may also illuminate the path for preclinical research.

### Acknowledgements

The authors would like to thank James Visanji, manager at Trilogy Writing & Consulting GmbH, and Anton Bespalov, managing partner at PAASP GmbH, for useful advice and discussion.

### 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 are employed by Trilogy Writing & Consulting (LPR) and PAASP GmbH (CE).

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# Nonclinical studies in the Russian Federation

## Problems, regulatory norms, and harmonisation with international standards

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### Abstract

Drug product developers and sponsors face a number of problems when organising a nonclinical study in Russia, especially, the diverse range of standards and few certified animal breeding centres, complicating adaptation of the available experimental data to domestic legislation. In this article, we discuss the main regulatory documents in Russia, their compliance with international standards (Good Laboratory Practice), the structure of the responsible authorities, and problems with implementing the regulatory documents. Finally, we discuss the current regulatory trends in Russian nonclinical studies.

### Laws regulating nonclinical trials in the Russian Federation

#### Federal Law No. 61-FZ

In the Russian Federation, Federal Law no. 61-FZ dated April 12, 2010,<sup>1</sup> is the principal document regulating the circulation of medicines. Paragraph 11 of this law defines the scope of nonclinical studies and requirements for performing them, including methods for assessing the quality, efficacy, and safety of a drug product. In addition, it stipulates the right to involve scientific and research institutions and relevant higher education organisations. It also requires that the study follows the approved plan and protocol so that the study results can be submitted to an authorised federal authority to



register the drug product. According to this law, nonclinical studies must follow the rules of laboratory practice approved by a relevant federal authority.

#### Implementation of Good Laboratory Practice (GLP)

##### *Decision nos. 2603-r, 2067-r, and 1172*

In Decision no. 2603-r dated December 28, 2012,<sup>2</sup> the Russian government approved implementation of the Organisation for Economic Co-operation and Development (OECD) GLP guidelines for test facilities (laboratories) conducting nonclinical studies. This was followed by Decision no. 2067-r dated November 8, 2013,<sup>3</sup> which specified the list of documents governing compliance of test facilities with the GLP principles. These documents are identical to the OECD's GLP and have been adopted in the Russian Federation as the national standards. In addition, Decision no. 1172 dated December 17, 2013,<sup>4</sup> specified the procedure for assessing test facility compliance with GLP principles.

Inspection, certification, and maintenance of the register of GLP-certified test facilities are handled by the Federal Service for Accreditation of the Ministry of Economic Development. As of August 1, 2017, this service had certified 10 test facilities, two of which were also accredited by the Slovak National Accreditation System.

##### *Decree no. 965*

Bringing the performance of nonclinical studies of medicines in compliance with the GLP rules is one of the tasks of the National Strategy for Development of the Pharmaceutical Industry (Pharma2020), which was established by the Ministry

of Industry and Trade of the Russian Federation in Decree no. 965 dated October 23, 2009.<sup>5</sup> The main goal of this programme was to create a modern system for developing and manufacturing medicines in the Russian Federation.

#### *"Guidelines for the Testing of Chemicals" from the Federal Agency for Technical Regulation and Metrology*

Following announcement of this programme and in response to Decision no. 2603-r and Decision no. 2067-r, in 2013–2014, the Federal Agency for Technical Regulation and Metrology developed an additional series of documents governing nonclinical studies. The new documents, "Guidelines for the Testing of Chemicals",<sup>6</sup> cover methods for assessing how a chemical affects the human body and, to a large extent, replicate the OECD Test Guidelines that are applicable to drug products. Currently, the Russian Federation has standards identical to Test Guidelines 402, 403, 406–408, 410–415, 421, 423, 424, 431, 452, 453, 471, 476, 477, and 487, which are available at <http://docs.cntd.ru>.

#### Standards for nonclinical studies based on International Conference on Harmonisation (ICH) documents

In the 2000s, the Ministry of Health of the Russian Federation issued some decrees on implementing GLP principles for nonclinical studies of medicines, and in 2015–2016, the Russian government introduced a series of the national standards entitled "Medicines for Human Use". Most of these standards are translated ICH documents (Table 1).

##### *Decree no. 199*

Currently, the only valid document regulating nonclinical studies is Decree no. 199 "On Approval of the Principles of Good Laboratory Practice" dated April 1, 2016.<sup>7</sup> This document contains general provisions correlating with the key national standards, GOST 33044-2014 "Principles of Good Laboratory Practice" and GOST R 53434-2009 "Principles of Good Laboratory Practice",<sup>8</sup> which are identical to the OECD's GLP. Decree no. 199 states that the GLP principles are applicable for all studies related to developing medicines, whereas Federal Law no. 61-FZ does not require a full compliance with these rules



**Table 1. National standards in the Russian Federation regulating nonclinical studies and their ICH equivalents**

Document	ICH equivalent
GOST 56700-2015 Medicinal Products for Human Use. Safety Pharmacology studies for human pharmaceuticals <sup>a</sup>	Similar to ICH S7A:2001 “Safety Pharmacology studies for human pharmaceuticals”
GOST 57147-2016 Medicinal Products for Human Use. Nonclinical evaluation for anticancer pharmaceuticals	Similar to ICH S9:2009 “Nonclinical evaluation for anticancer pharmaceuticals”
GOST 57146-2016 Medicinal Products for Human Use. Studying for carcinogenicity of pharmaceuticals and excipients	Contains main regulatory provisions of ICH S1A:1995 “Guideline on need for carcinogenicity of pharmaceuticals”; ICH S1B:1997 “Testing for carcinogenicity of pharmaceuticals”; ICH S1C(R2):2008 “Dose selection for carcinogenicity studies of pharmaceuticals”
GOST 57130-2016 Medicinal Products for Human Use. Genotoxicity testing and data interpretation <sup>b</sup>	Similar to ICH S2:2011 “Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use”
GOST 56702-2015 Medicinal Products for Human Use. Nonclinical toxicology and pharmacokinetic studies of safety	Contains requirements of ICH S3A:1994; ICH S3B:1994; ICH S3A “Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies”; Section 5: ICH S3B: “Guidance for repeated dose tissue distribution studies”
GOST 56699-2015 Medicinal Products for Human Use. Preclinical safety evaluation of biotechnology-derived pharmaceuticals. General recommendations	Similar to ICH S6 (R1):2011 “Preclinical safety evaluation of biotechnology-derived pharmaceuticals”
GOST 56701-2015 Medicinal Products for Human Use. Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals	Similar to ICH M3(R2):2009 “Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals”
GOST 57129-2016 Medicinal Products for Human Use. Part 1. Stability testing of new drug substances and products. General recommendations	Similar to ICH Q1A:2003 “ICH Topic Q1A (R2) Stability Testing of New Drug Substances and Products. Part 1. Stability testing of new drug substances and products”

<sup>a</sup> Title changed to correspond to those adopted in the “Medicinal Products for Human Use” standards.

<sup>b</sup> Applicable only for chemically synthesised medicines, not valid for biological products

when screening and evaluating the active substance. In other words, paragraph 11 of the Federal Law no. 61-FZ conforms with international practice, which is to not regulate pilot medical and biological studies conducted during research and development.

The need to adhere to the quality standards at the initial R&D phases is clear, but the legal framework in the Russian Federation does not include principles similar to the quality standards for biomedical studies. Despite this, safety is a key aspect of GLP; they require assessing the public and ecologic safety of chemical substances, including medicines. Applying GLP principles to the development of medicines, as

required by the Ministry of Health, may lead to the loss of sources, prolongation of studies, repression of progress and block of new approaches, etc.

#### **“Guidelines for Preclinical Trials of Medicinal Products”**

Since 2000, the Scientific Centre for the Expert Evaluation of Drug Products for Human Use, which is part of the Ministry of Health, has provided expert review of planned clinical trials, related documents, and registration dossiers. The Centre produces compilations of their recommendations on nonclinical studies of medicinal products. Their latest document,

“Guidelines for Preclinical Trials of Medicinal Products”, which comprises two volumes, was released in 2012.<sup>9,10</sup> The first volume contains, in addition to a list of known and well-proven tests, recommendations on evaluating the safety of prospective drug products.<sup>9</sup> According to these recommendations, the safety of the original drug product, its mechanism of action, and acute and sub-chronic toxicity should be demonstrated using two animal models, one of which is non-rodent. In addition, the recommendations require providing data on immunotoxicity, reproductive toxicity, embryotoxicity, mutagenicity, carcinogenic activity, cumulative properties, sensitising activity, pharmacokinetics, and metabolic effects.

The second volume of “Guidelines for Preclinical Trials of Medicinal Products”<sup>10</sup> defines the scope of obligatory safety evaluation studies for bio- and nano-technological drug products, combined drug products, galenic formulations, paediatric drug products, and generics. According to these Guidelines, to comply with GLP requirements, nonclinical studies must be performed for both the active pharmaceutical substance and its finished dosage form. Even though the Centre’s compilations do not have regulatory status in Russia, local drug developers consider them mandatory.

#### **Federal Law no. 429-FZ**

On July 1, 2015, amendments to Federal Law no. 61-FZ, defined by Federal Law no. 429-FZ,<sup>11</sup> came into force. Law no. 429-FZ takes into account the need for federal approval of rules for proper pharmaceutical practices, including GLP. The amendments do not directly affect nonclinical studies, but it introduced new terms (e.g. orphan drugs, biological preparations, and bioanalogs) and their definitions. This led to implementation of new approaches and methods for nonclinical research. The new law also introduced scientific consulting procedures for issues related to nonclinical and clinical research, assessing drug quality, evaluating efficacy and safety, and registering medications.

### **Barriers to implementing the guidelines**

In summary, for nonclinical studies of drug products, the investigators and the study teams must follow:

- GLP rules,
- the set of documents approved as national standards and compliant with the OECD, the ICH, and Decree No 199N, and
- Guidelines for Preclinical Trials of Medicinal Products.

Several problems have created barriers to implementing all these guidelines, including inconsistencies in toxicity study designs, inconsistencies in terminology, and an insufficient supply of good-quality animals.

#### **Inconsistencies in toxicity study designs**

A number of problems arise in applying recommendations because of inconsistencies between the standards set forth in “Guidelines for the Testing of Chemicals”<sup>5</sup> and tests traditionally used by Russian investigators and

experts. For instance, in Russia, acute and single-dose toxicity studies are not seen as different. As a rule, acute toxicity experiments allow the lethal dose to be determined exactly or at least to be approximated, but the OECD methods do not always require a 50% lethal dose to be determined. According to the “Guidelines for Preclinical Trials of Medicinal Products”,<sup>9,10</sup> which is strictly followed by experts of the Ministry of Health, the 50% lethal dose (LD50) should be determined by the Litchfield and Wilcoxon method,<sup>12</sup> and cumulative properties of the drug product should be determined as suggested by Lim et al,<sup>13</sup> which depends on the LD50. The guidelines also state that for studies in large animals, even if the LD50 has not been determined, describing only the toxic effects is allowed and that small animal studies should not be continued at higher doses if death has not occurred at 2000 mg/kg. In other words, determine the LD50 is not always necessary according to the OECD.

ICH M3R2, adopted as the national standard in the Russian Federation (Table 1) recommends performing an extended single-dose toxicity study. In addition to evaluating acute toxicity, such studies determine clinical, chemical, haematological, haemostatic, toxic, kinetic, and other parameters. They provide a wider overview than the common approach and results that are compatible with those obtained by repeat-dose studies. In the most cases, single-dose toxicity can be evaluated in escalation-dose or in short-dose experiments. To predict short-term safety in people, toxicity is evaluated according to ICH S7A and S7B, which are identical to the national standard in Russia (Table 1). However, investigators usually choose to comply with the “Guidelines for Preclinical Trials of Medicinal Products”,<sup>9,10</sup> as recommended by the Ministry of Health, which do not use the term “pharmacological safety”, and investigators rarely perform the types of study described in the ICH guidelines, evaluate the maximum tolerated dose in a repeat-dose experiment, or perform individual safety experiments. At the same time, the more recent “Guidance on Expert Assessment of Medicinal Products”<sup>14</sup> states that the safety of a drug product must be evaluated before the first-in-human studies.

**Despite barriers to implementing the guidelines, the Russian Federation is gradually beginning to understand that without common standards, new treatments will not become available.**

#### **Terminology inconsistencies**

Inconsistencies in terminology has been an important barrier to introducing GLP principles in the Russian Federation. For example, the Decree no. 199n<sup>7</sup> and the Federal Law no. 61-FZ<sup>1</sup> use the term “preclinical studies”, whereas GOST 33647-2015 uses the more correct term “nonclinical studies”.<sup>15</sup> The term “preclinical studies” assumes that all respective studies are completed before the first administration of a drug in human, whereas most of them are conducted at the same time as the clinical trials.

A standard for terminology, GOST 33647-2015,<sup>15</sup> has been developed and includes terms consistent with the GLP definitions for nonclinical safety studies of chemicals, provided in both Russian and English.

#### **Insufficient supply of good-quality animals for nonclinical studies**

Another barrier to implementing GLP principles in Russia is the lack of a sufficient supply of animals. Only the “Pushchino” animal breeding centre of the Institute of Bioorganic Chemistry of the Russian Academy of Sciences has an international veterinary certificate, and until recently, animal breeding centres at research institutes were the only sources of laboratory animals. In addition, due to a lack of funding, breeding facilities have been poorly maintained or abandoned. Although GLP studies cannot be performed without SPF animals, they are bred at only two centres in Russia. Furthermore, the range of animals is limited because no centres breed cats or dogs, only one breeds primates, and only a few breed ferrets, gerbils, and mini pigs.

### **Going forward**

Despite barriers to implementing the guide-lines, the Russian Federation is gradually beginning to understand that without common standards, new treatments will not become available. Members of the Eurasian Economic Union, which includes Russia, Belarus, Kazakhstan, Armenia, and Kyrgyzstan, have compiled common regulatory requirements and have therefore developed legal regulations for the circulation of medicines. The Union has created a unified system for drug registration, is discussing issues related to

inspections and mutual recognition of preclinical (nonclinical) and other research, and has translated and adopted nearly all appropriate European pharmaceutical practice guidelines. GLP principles have been developed taking into account the approaches adopted by the European Union, OECD, and ICH.

## Conflicts of interest and disclaimers

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

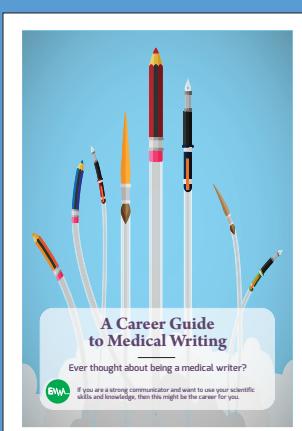
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## Abstract

While Brexit has brought about a period of uncertainty in the UK's pharmaceutical industry, what is an appropriate response by medical writers at such a time? Few successful businesses stand idle and wait for things to happen. Taking a look at the current climate of outsourcing and the UK's business environment in terms of investment, now may be the time for writers to consider their strengths and weaknesses, diversifying their portfolio, and being strategic in seeking a competitive advantage.

Britain's decision to leave the European Union is one that has stunned the small business community, with many unwilling to offer opinion on an issue where seemingly the only certainty is uncertainty. Brexit is simply unprecedented: No nation has previously taken the step to leave the EU, meaning that there is no body of literature and no data to be consulted. Moreover, as the terms of Brexit have yet to be negotiated, and there have been very few assurances as to what form they may take, businesses have an uncomfortable situation of limbo; unsure as to what the effects of Brexit will be for their industry. However, through an assessment of probable Brexit scenarios and their effect on the medical writing industry, the relevant literature, and the views of industry professionals, we shall attempt to extrapolate some generalisable principles that may be helpful in navigating through such uncertain times. The dominant impression is that medical writers should prepare to face greater competition from abroad, with

pharmaceutical companies being increasingly willing to outsource to countries, such as India. Yet, greater competition does not necessarily mean that British medical writers will have to surrender their market share, as the effects of greater competition may be mitigated for by means of acquiring a competitive advantage: In the case of UK medical writers, this is likely to involve convincing the pharmaceutical companies of their superior level of service.

## Brexit: Significant effects

Perhaps the most universally accepted claim about Brexit is that its effects will be significant and will doubtlessly have a profound impact on UK businesses, particularly those which rely on foreign investment. Cumming and Zahra argue that "Brexit is a monumental event that is likely to have serious consequences, raising challenges while creating international business and entrepreneurship opportunities for companies around the globe".<sup>1</sup> On the positive side, the UK will be able to negotiate a set of mutually beneficial trade deals with whomever it chooses, whether this be the US or even China. Besides, the eventual outcome of the negotiations will probably result in the removal of several EU regulations and tariffs, which could allow UK businesses to cut costs and accelerate transactions, hereby improving efficiency. Furthermore, the decline in the value of the pound could make the UK more attractive to foreign investors, particularly from non-EU countries like the US.<sup>1</sup> Thus, it might be argued that a change of this magnitude may create opportunities that were not previously available to UK companies.

## Fall in the pound

While the decline in the value of the pound may have a positive effect on those companies exporting goods and services, any businesses more reliant on imports are likely to see the opposite effect: Increased costs of goods and services, which could have a detrimental effect on the UK economy.<sup>2</sup> Furthermore, the climate of uncertainty surrounding the Brexit negotiations could dissuade companies from

investing, with some already considering pulling out of the UK.<sup>3</sup> Moreover, whilst on the one hand, withdrawal from the EU will also involve withdrawal from EU regulation, tariffs, and "red tape", it will also bring with it new regulatory challenges. Although possible, the UK is unlikely to retain its free trade agreement with the EU, meaning that it may have to individually negotiate deals with each EU nation that it seeks to retain economic ties with and seek to negotiate new trade deals with other nations. Without doubt, this will have a considerable effect on UK businesses, particularly those with a more global focus and the medical writing industry will be no exception to this.

## Foreign investment: Effect on outsourcing

Lowendahl demonstrates that the impact of Brexit on foreign direct investment to the UK largely depends on the type of investment.<sup>3</sup> However, he also observes that one type of operation that will probably be most affected is outsourcing, particularly that of knowledge-based services. Lowendahl propounds that, in this case, investors are attracted to the UK by the fact that the free movement of people in the EU allows them to access the greatest pool of talent and technical expertise from across Europe. Traditionally, the UK has had a consequential competitive advantage over other EU nations regarding knowledge-based services because many companies, including pharmaceuticals, choose to operate largely in English. Nevertheless, Lowendahl argues that "the UK's attractiveness for FDI [Foreign Direct Investment] in knowledge-based services sectors is likely to be seriously at risk if the UK does not agree to freedom of EU nationals to work in the EU", as the UK will no longer be able to guarantee the greatest pool of talent from across Europe.<sup>3</sup>

## Effect on drug research and medical writing

A sample canvassing of recruiters working closely with both pharmaceutical companies and medical writers found that, as English





remains the language of choice for medical writing, the UK still has a competitive advantage, with much of the European writing talent being based in the UK. This being said, when it comes to regulatory and life sciences, a significant amount of the talent comes from Europe, meaning that the free movement of people is vital in maintaining Britain's position at the forefront of research. While the UK government has acknowledged the seriousness of this need, recruiters continue to assert just how much the UK cannot afford to lose this free movement of people in the life sciences.<sup>4</sup>

In terms of implications for the pharmaceutical industry itself, Brexit will doubtlessly have a serious impact. On the face of it, pharma may seem like a safe industry, as people will always be ill and hence always need drugs, regardless of the economic climate. Moreover, generally in times of economic strife, healthcare spending remains largely protected. Despite this, politicians will seek to cut what they can and one of the areas most vulnerable to this is drug innovation and which drugs the National Health Service (NHS) can afford to use. Currently, the UK is Europe's foremost destination for Phase I trials. However, as the UK will no longer be

eligible for EU grants and able to participate in EU-wide projects, this could be about to change.<sup>5</sup> Furthermore, the UK is probably going to have to change its regulatory body from the European Medicines Agency (EMA) to the UK's Medicines and Healthcare products Regulatory Agency (MHRA), which, although the two bodies are closely aligned, will presumably create further disruption, especially if marketing authorisations in the EU are no longer automatically valid in the UK.<sup>6</sup> Given that medical writers play an intrinsic role in the process of drug marketing applications, the implications for them could be equally significant. Articles on Brexit posted on The Organisation for Professionals in Regulatory Affairs (TOPRA) website,<sup>7</sup> reveal a reluctance to commit to any clear stance from both regulatory

bodies, with the EMA saying that "The implications for the seat and operations of EMA depend on the future relationship between the UK and the EU. This is unknown at present and therefore we will not engage in any speculations".<sup>8</sup>

### **Outsourcing medical writing to other English-speaking countries**

More broadly speaking, Brexit must be viewed within a wider context: The increasing willingness of pharmaceutical companies to outsource medical writing to countries where it is simply cheaper to do so, India being the most prominent example. It might be noted that Brexit may simply accelerate a process that has already been occurring for several years. With the future changes in regulatory bodies and a probable decrease in the talent pool, the UK becomes a less attractive place for the industry to outsource their medical writing. Now, instead of being able to rely on contracts for potentially a year at a time, UK medical writers may notice they can only be assured work for a matter of months.

The overall picture for UK medical writers, consequently, does not seem overly positive.

**Alongside the ongoing demands of running a small business, continuous professional training development is often an area neglected by independent medical writers.**

Although the continued success of the UK medical writing industry is threatened, this is not to say that there are no positives to be found from Britain's decision to leave the EU for UK medical writers.

First, it is important to note that the UK has not yet left the EU and, in the short term, medical writers may benefit from the decline in the pound's value, medical writing effectively being an exported service. Additionally, it might be observed that the UK medical writing industry has enjoyed incredible success over the past few years, with medical writers often being offered so much work that they have to turn some contracts down; it is only natural that such a monopoly over the industry could not last forever. The result of this process is that UK medical writers might well now have to compete in order to secure contracts from pharmaceutical companies, as is normal in almost any other industry. Hence, the implications of Brexit are not catastrophic or devastating, but merely dictate that UK medical writers will now have to work harder to secure a competitive advantage over their rivals.

### The competitive advantage for UK medical writers

According to Winer (2004), securing a competitive advantage relies on three principles. The first of these is customer value, which "can be defined by the customer in terms of lower price, speedy delivery, convenience, or some other characteristic"<sup>9,10</sup>. However, as UK medical writers are unlikely to be able to compete with India in terms of price, to ensure customer value they shall have to rely on both efficiency and convenience. For instance, agreeing to more ambitious timelines or agreeing to night-time working to accommodate different time zone working patterns.

The second is the enhanced value of the product and it is important to add that this point is, at least partially, perception based: It does not necessarily matter if the service provided is actually better than that provided by competitors, but merely that it is perceived to be so. Traditionally, UK medical writers have had an intrinsic advantage here, as not only is most medical writing written in English, but



pharmaceutical companies have been able to rely on the UK having the best pool of talent from across Europe. For instance, review meetings conducted by a native English speaker with many years of medical writing experience can be perceived as a significant advantage to a study team. Even so, if the result of Brexit is the removal of the free movement of people and attendance in person at certain meetings is expected, then this will no longer be the case, meaning that UK medical writers will have to convince the pharmaceutical industry of their superiority through some other means.

Thirdly, UK medical writers are unique in that they are working and writing in their mother tongue. They also bring many years of experience of working specifically within the UK and European regulatory arena together with the benefits of a good international network of medical writers fostered by organisations such as EMWA.

### How to build an image of superiority

Alongside the ongoing demands of running a small business, continuous professional training development is often an area neglected by independent medical writers. There is a danger of being caught out by a new regulatory guideline; for example, the new demands and

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document standards required for pharmaceutical vigilance, or the dossier requirements for China. There are many newer niches that have developed in the past few years that are as well to be aware of and prepared to write for. Reading the regulatory literature and following relevant blogs can keep awareness keen. Training and flexibility are likely to be attributes that build the perception of superiority alongside numbers of years of experience.

Given that superior service is at least partially based on perception, perhaps one of the most important methods by which UK medical writers may impress pharmaceutical companies is through the quality of their curriculum vitae (CV). This may be taken for granted by many, but in an environment where medical writers have had very little competition, the necessity for a polished CV has been somewhat diminished. Furthermore, the concept of presenting oneself well ought to extend to pages on sites such as LinkedIn. Profiles may need to be updated and improved if UK medical writers expect to obtain and secure a sustainable competitive advantage.

Having a polished CV and a professional profile on LinkedIn is of little use, however, if it bears no relation to reality; in other words, superior service should not only be perceived, it must actually be up to standard. One way by which this may be achieved is through having a superior workforce and holding them to high standards, making managerial direction supremely important. Furthermore, a more competitive environment may require medical writers to be more proactive in seeking contracts from pharmaceutical companies, instead of waiting to be sought out by recruitment companies. It may also be necessary to be willing to take a more diverse range of contracts for two reasons. First, any investor will tell you that diversification results in greater protection from risk, and in such uncertain times perhaps this has never been more applicable or more poignant for medical writers. Second, diversity ensures individuality: If a medical writing company is willing to accept contracts that others are not, it thus ensures a competitive advantage, which is Winer's third point relating to uniqueness.

## Conclusions

If UK medical writers are to survive the post-Brexit environment, then they must be prepared to face more rigorous competition. Competition should only be detrimental to those businesses who either fail to provide good service, or fail to convince their clients of the quality of service that they provide. Therefore, if British medical writers continue to demonstrate their importance to the pharmaceutical companies, then they are likely to thrive in an increasingly competitive environment. It is also important to note that simply because Brexit has brought with it so much uncertainty, medical writers should not stop planning to grow and diversify their businesses, as “the alternative is planning to stagnate”.<sup>11</sup>

## Acknowledgements

Thank you to Daniel Clifton, Katarzyna Koscielecka, and Tim Jenkins for contributing their views and/or help with this opinion piece.

## Conflicts of interest

The authors have no conflicts of interest to report.

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# Creation of a patient-centric patient lay summary in the local language

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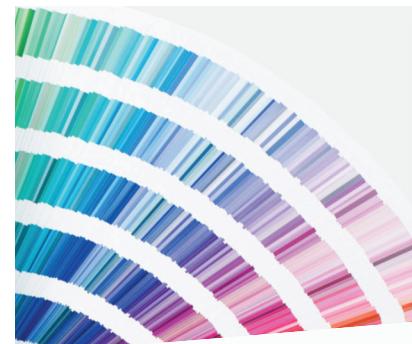
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## Abstract

Prior to this project, no patient lay summary (PLS) had ever been developed locally in Japan. In order to create a PLS that is more tailored to local patients, we attempted to develop one in and for Japanese. Such PLS was drafted based on the disclosed summary of the clinical study report. We took a composite approach in refining the PLS by researching on lay language and patient-friendly designs. At the same time, we ensured scientific accuracy through consultation with experts such as physicians and statisticians, practised diligence on regulatory and legal aspects, and incorporated patient's voice by consulting a local patient advocacy group. We successfully created a PLS in the Japanese language for the first time, which was more patient centric than those translated from another language.

While summary results of clinical trials have commonly been posted on global websites such as clinicaltrials.gov<sup>1</sup> and EU Clinical Trials Register,<sup>2</sup> the European Union Clinical Trial Regulation No. 536/2014<sup>3</sup> states that sharing clinical trial results to study participants in the form of a lay language summary is also an important endeavour. In Japan so far, we have distributed patient lay summaries (PLSs) for two clinical trials,<sup>4</sup> which were originally written in



## この治験の経緯

日本で実施したこの治験には、25の医療機関から122名の患者さんが参加されました。当社は、この治験のデータをもとに、この薬の働きに関する結果報告書を作成しました。この「治験結果のまとめ」はその結果報告書をわかりやすくまとめたものです。



## ご協力、ありがとうございました！

このたびは、治験にご参加くださり誠にありがとうございました。この治験は2009年5月に開始し、2014年12月に終了しました。あなたを含む100名の患者さんにご参加いただき、疾患に対するこの薬の働きを調べました。この治験の実施を依頼した当社は、この治験にご参加・ご協力してくださったみなさまに治験の結果をお知らせすることは、とても重要であると考えており、この「治験結果のまとめ」を作成しました。このまとめをお読みいただくことで、みなさまが新しい治療法の開発に貢献されていることを知っていただければ幸いです。

English and translated into Japanese by an external organisation. In order to create PLSs that are more tailored to local patients, we have pioneered creating a Japanese PLS starting from scratch.

We formed two teams: One was responsible for researching on the characteristics of lay language, developing a template, communicating with a patient group, and considering legal and regulatory aspects; the other took charge of drafting a PLS. The two teams collaborated in refining the PLS and developing a process of PLS preparation. The team members voluntarily participated in the project and were consisted of medical writers and members of the document management group.

## Developing the template

To develop a patient-friendly template, we first gathered patient information materials at local hospitals and clinics and critically evaluated their designs concerning legibility and readability. We also looked for relevant guidelines and design principles. We adopted the concept of "universal design" for effective communication<sup>5</sup> and in particular considered the following aspects:

- Font and style of text: We

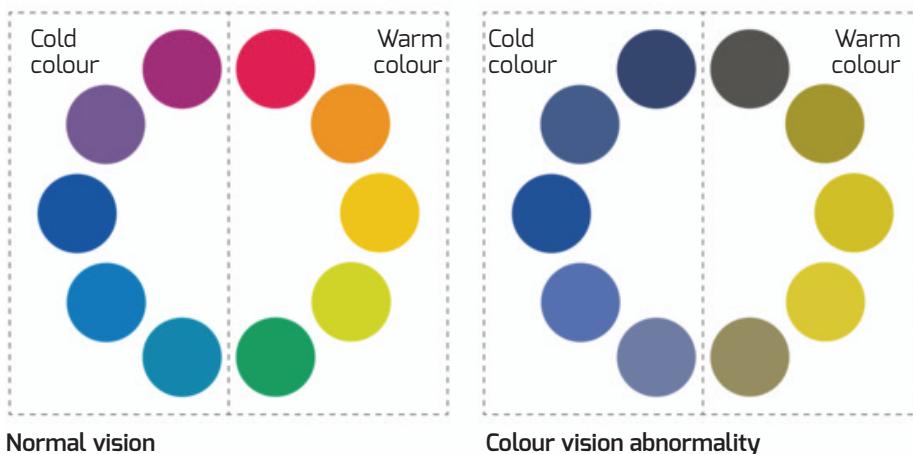
chose to use a recommended Japanese font Meiryo primarily, as it has a very clear typeface that maintains high legibility even in bold style. Also to enhance legibility, we used a font size larger than what we would normally use for regulatory documents (i.e., 12-point size was used for the main text of the PLS while 10.5-point size would normally be used for regulatory documents).

- Line spacing: Wider line spacing was used to optimise legibility and readability. This also allowed us to place a Japanese reading aid (in form of syllabic scripts) above some Kanji characters, which are similar to Chinese characters, in order to show how this text should be read. This was a part of the attempt to keep the language level equivalent to a Japanese junior high school graduate.

- Colours: In particular, a barrier-free colour scheme (see Figure 1) was studied to make sure that even patients with colour vision abnormality can appreciate the PLS without difficulty. People with colour vision abnormality have difficulty differentiating among cold colours or warm colours. For instance, it is hard for them to distinguish between red and green, purple and blue, or orange and yellow.

We adopted the concept of "universal design" for effective communication.

**Figure 1.** A colour scheme comparing how people with normal vision and with colour vision abnormality perceive cold and warm colours based on Takahashi and Katayama.<sup>5</sup> (Reprinted with permission)



- Page layout of text sections: Text headings and special messages such as “thank you” should be easily discernible. This also allows readers to easily navigate through the PLS. Although the primary purpose of distributing a PLS to patients is to share clinical trial results, it also provides pharmaceutical companies the opportunity to convey their appreciation of patient participation in a study.

Aside from the points suggested by the universal design concept, we believed that the appearance of the overall printed form of a PLS was also important as it is intended for persons in already stressful situations. For instance, an accompanying image in a text can appeal to viewer’s senses and stir positive emotions, which

can consequently alleviate the stress associated with illness. In this case, we chose the image of dandelions (Figure 2) because it is not only a flower familiar to many, it also has a bright colour and is very resilient. It has been used as a symbol of courage in many cultures and could represent clinical trials spreading “seeds” of possibilities. Further, we made sure that the picture followed a barrier-free colour scheme (i.e., predominantly blue and yellow), and did not use brand colour or image so that it could be applied to any drug in Pfizer.

We also identified standard texts (e.g., “thank you” message, headings for an introduction, background, etc.) for the PLS and inserted them in the template as default texts. Moreover, we

**Figure 2. Picture used in our patient lay summary.**

(Japanese text translation: “Dandelions spread their seeds when the wind blows. Clinical trials spread seeds of possibilities for a healthier world through your cooperation.”)



風に種を乗せて多くの花を咲かせるタンポポ ——  
治験は皆様一人ひとりのご協力により、  
より健康な世界への「可能性の種」を広げています。\*

followed the advice of our legal department, in which we incorporated the following information into the template:

- The date of document creation at the end of the template to control document versions and prevent any post-approval revisions; and
- A cautionary statement requesting patients to refrain from posting on social networking service, etc.

## Drafting

We drafted the PLS based on the Public Disclosure Synopsis as posted on the Pfizer website.<sup>6</sup> As reference for Japanese lay language, we used informed consent documents (ICDs). A comparison of the drafting process between the previous and our current model is shown in Figure 3. In our current model, no external organisation was involved (i.e., solely authored by Pfizer Japan). Aside from paying particular attention to the above mentioned aspects of design, language and structure, and not being promotional, the draft was reviewed by in-house experts (e.g., physicians, statisticians, legal and regulatory experts) and principal investigators to ensure scientific accuracy and suitability for public disclosure. It is important to mention that we also sought feedback from a patient advocacy group that had no direct involvement with the clinical trial.

Finally, we used the following checklist of questions to ensure that the PLS was patient friendly in both format and content:

- ✓ Is it easy to understand?
- ✓ Is the language level of the content equivalent to that expected from a Japanese junior high school graduate?
- ✓ Are there arbitrary statements?
- ✓ Are there any inappropriate words?
- ✓ Can patients understand accompanying charts effectively?
- ✓ Is the text length appropriate?
- ✓ Are the font size and colour scheme appropriate?
- ✓ Are illustrations appropriate?

## Delivery to patients

The PLS was posted on the Pfizer Japan’s website<sup>7</sup> in PDF format and protected by a password. The link and the password were provided to the study participants at clinical trial sites.

**Figure 3. Two different processes of creating a PLS in Japan**

(PLS= patient lay summary; NPO= non-profit organisation; PDS= Public Disclosure Synopsis; PI= principal investigator)



## Feedback from a patient advocacy group

Overall feedback was favourable and are summarised as follows:

- Easy to read
- Very polite writing and well organised (starting with the “thank you” message, then moving on to the background of the trial, the rationale for research, the method, and the results)
- Generally, easy to understand due to the explanations provided before or after technical terms such as placebo and adverse event
- Warm and soft image of the dandelion suited to alleviate patients’ pains due to illness

With these comments, it appeared that the locally developed PLS was more patient centric in language, content, and design. Using the local language from the drafting stage additionally made it easier to create a PLS that is more culturally and ethnically appropriate and thus suited the sentiment of local patients.

The previous lay summaries of the two other clinical trials, which were translated from English, were highly appreciated by patients at clinical study sites,<sup>4</sup> as there had been no other attempt to provide patient access to clinical trial results. The PLS directly created in Japan received more favourable feedback because it did not only provide information but also presented the information better. In this way, the impact of PLS on patients was stronger.

We believe that enhancing patient literacy on drug development would help advance patient centricity in the pharmaceutical industry. Distributing the PLS would serve as a great opportunity to educate patients about clinical trials, helping us form a win-win relationship in drug development. In addition to giving patients access to the clinical trial results, further involvement of patient advocacy groups in preparing clinical trial related documents such as ICDs would also contribute to foster a culture of trust between pharmaceutical companies and patients. Increased transparency as regards clinical trials and their outcomes would allow us to conduct clinical trials more effectively and ultimately lead to the acceleration of drug development.

## Recommendations

Because the PLS is not a regulatory document (e.g., clinical study report) and is intended for patients, we need to be particularly careful in stating conflicts of interest and in refraining from being promotional in both content and tone. Indeed, as more steps were required to ensure the non-promotionality of a PLS, it took a longer time to finalise the PLS than any regulatory document.

To prepare a PLS more efficiently in the future, we identified a few areas that need to be improved or explored:

- Establishment of an effective way to confirm that the PLS is not violating the promotion code

- Ensuring compliance with local regulations and practices
- Assessment of medical and statistical appropriateness in paraphrasing technical content in lay language
- Finding an effective way to involve principal investigators
- Establishing a good relationship with patient advocacy groups in Japan
- Increasing patient involvement in preparing the ICDs to promote patient centricity
- Collaboration with regulators to establish a framework for clinical trial results disclosure in the industry
- Improvement of medical writing skills in lay language/ local language

We believe that industry-wide efforts are necessary to achieve these points effectively.

## Conclusions

We successfully created a PLS in the Japanese language for the first time. The locally developed PLS was more patient centric than those translated from other languages, allowing us to communicate clinical trial results in a more patient-friendly manner and helping us to form a better relationship with patients. Using the patients’ local language and being culturally sensitive are one of the most patient centric activities pharmaceutical companies can undertake.

We hope that our current attempt in developing a PLS locally would help trigger an

increase in the distribution of such summaries in Japan. We believe that locally developed summaries would bring more benefits to both patients and the pharmaceutical industry, especially in more culturally and linguistically diverse regions such as the EU.

## Conflicts of interest and disclaimers

The authors are employed by Pfizer Japan Inc.

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# Six communication rules for scientific presentations and writing



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## Abstract

In our daily work as coaches and writing trainers, we often work with young scientists who are at the beginning of their careers. When they want to publish their first scientific research paper or when they decide to give their first lecture at an international congress, they perceive these challenges as hurdles that need to be overcome separately. They might think that each of these tasks, writing and presenting, has its own rules and requirements that need to be learned and internalised. In our consulting practice, however, we often feel that the same principles apply to both scientific writing and presenting. Therefore, we have defined the following six communication rules.

## 1. Winning the start with the first impression

With a successful start, you win the audience over to your side. With a bad entry, you might scare them away. It is just like a dating situation: the first impression influences whether you will get a chance to make a second impression. The introduction determines the way in which people will experience your text or talk. It influences whether your listeners and readers expect an interesting or a boring story.

A successful introduction always piques the readers' and listeners' curiosity and their desire for more. Hence, you should not begin your text or talk with commonplace information that medical students have already learnt during their first term – for example, “Parkinson's disease is a chronic and progressive neurodegenerative disease.” It is more appropriate to emphasise the focus and significance of your specific research project – for example, “Heterozygous glucocerebrosidase mutations have emerged as the leading genetic risk factor for Parkinson's disease.”

In a lecture, this content level is augmented by the personal level: Only those who are enthusiastic and motivated when entering the stage can inspire and motivate their audience. How does one get to be enthusiastic and motivating? A piece of advice that might initially appear ridiculous is to smile. According to the facial feedback hypothesis, smiling for one

minute can enhance your mood demonstrably.<sup>1</sup>

<sup>2</sup> Another and perhaps more sustainable method is to focus your mind on the following questions:

- What inspires me – in general and in my research?
- What is the benefit of my work?
- What does it make possible, easier, or better?

These questions help you to focus on the positive aspects of your work. In addition, the third question might lead to an interesting opening to your lecture or text.

## 2. Keep the story simple

Both presentations and research papers must not be overloaded with details or aspects that contribute nothing to the story of your project. The easier and more straightforward your data are explained, the more inviting your story will be to the audience. On the contrary, if a presentation or text is too complicated and difficult to understand, the listener or reader will intuitively suspect methodical weakness and poor data.

In typical lines of reasoning in both scientific writing and presentations, a question leads to an answer or a problem leads to its solution. Especially in a lecture, things should be explained as simply as possible ( $x = 2$  instead of  $2x = 4$ ) as the listener, in contrast to the reader, cannot page back. Once the connection between speaker and audience is lost, it is difficult for your audience to

keep up with the presentation. Therefore, you should deliberately use the stylistic means of repetition, because key words and key phrases help the listener to keep on track. It might be additionally useful when things are illuminated from different angles because two different perspectives create multidimensionality.

### 3. Structuring

Structuring and outlining is essential when you prepare the storyboard of your text or presentation. IMRAD is the most common macro-structure for scientific articles and presentations (Introduction, Methods, Results, and Discussion). SCORE<sup>3</sup> is another method for scientific presentations: Symptoms: What is the problem? Cause: What is its cause? Outcome: What is my goal? Resource: How do I solve the problem? Effect: What is possible now? Both macrostructures lead the reader and listener through the story of a scientific text or presentation in a logical way.

In addition to the macrostructure of texts and presentations, there is a microstructure equally important for comprehension and convincibility for both texts and presentations. This micro-structure refers to both paragraphs and presentation slides. It starts with the topic providing an overview of the details that follow, then presents the details supporting the topic, and ends with an optional summary or concluding remark. In both scientific writing and presentations, the topic might be a message or question. Details are then presented in supporting sentences, bullet points, or figures. At the end of the paragraph or presentation slide, the information may be summarised in simple words to move from one paragraph or slide to the next. Another principle that applies equally to both texts and talks is that each paragraph and slide must be limited to one single major point or idea. Any deviation from this principle would mislead the reader or listener and ruin your main point.

### 4. Keeping the audience's attention

Your audience is like a tender plant that needs to be sheltered and maintained by, for example, simple linguistic means. Thus, authors and speakers should avoid the passive voice, excessive nominalisations, and negative expressions.

In contrast, they should write and speak in the active voice and use lively verbs. A pause can also stimulate the tension and alertness of the audience. This pause can be a moment of silence during your talk or a dash in your text.

Another tool to grab the attention of the audience is images. These are not only real pictures such as illustrations and tables, which are known to tell more than a thousand words, but also linguistic images. If you think that these metaphors are a taboo for scientists, you are wrong. Think of the "lock and key" complemen-

**Both presentations and research papers must not be overloaded with details or aspects that contribute nothing to the story of your project.**

tarity of antigen-antibody reactions, the sugar-phosphate "backbone" of DNA, and the so-called "housekeeping" genes. These metaphors have long been a part of the scientific language – many of them are even more effective in communication than a stylish and fancy presentation slide.

In a lecture, emotions can additionally capture attention – by inspiring, amusing, or surprising. Why not present the story of your project like a movie? Was it a drama? Did you feel lost, like in Cast Away? Alternatively, was it an action movie, like Outbreak? Only those who are emotionally involved can take their audience on a long journey.

To illustrate this journey during your talk, do not be too static and do not stick to the lectern. Just take a few steps towards the audience, then perhaps to the left, to the right, and finally back to the lectern – but stay authentic. It helps to place the flip chart at the opposite end of the stage or to use your hands instead of the laser pointer to indicate the points of interest on your slide.

### 5. Check the tech

Familiarise yourself with the technical requirements before you start your lecture or your writing project. It is annoying to have to postpone your talk because the data source, laser pointer, microphone, or whiteboard marker does not work. It is equally annoying when the submission of your manuscript is delayed because the software does not do what it is supposed to do.

### 6. Practice, practice, practice

One day you wake up and overnight you have become a gifted speaker or talented writer – that

is not likely to happen. Both presenting and writing need to be trained and practised constantly – not only when the writing project or the lecture is imminent. Regular training, such as the writing of protocols and laboratory notebooks as well as regular presentations in front of your colleagues, will improve your skills and enhance your self-confidence. Additionally, the feedback from friends and colleagues or by means of a video recording will help.

If scientific writing and presenting were sports, these six communication principles presented here would certainly be part of the training. So, stay tuned; it is worth it.

### Conflicts of interest

The authors declare no conflicts of interest.

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# So, you want to be a medical journalist?

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## Abstract

What are the differences between medical journalism and medical writing? To find out, the authors reviewed several health-related publications and online resources, and interviewed two senior medical journalists. We learned that medical journalism demands an investigative nature, the ability to critically evaluate evidence, and the ability to rapidly produce engaging pieces of wide interest. It is a stimulating, sometimes fast-moving world, although often not well-paid. Print media is becoming less common, and most journalistic pieces are now published online or through social media. For those interested in a new career, excellent writing skills and an ability to learn quickly are probably more important attributes than journalistic qualifications. Would-be medical journalists should keep in mind that with this power to influence comes responsibility.

## Introduction

Many medical writers look over the fence at the world of medical journalism and wonder what it is like and how some have reached prominent positions in leading publications or on TV. In this article, we explore the differences between medical journalism and medical writing and what attributes are important for someone interested in becoming a medical journalist.

## Medical journalism is the same but different

Headlines such as “Antibiotic resistance now a global threat”,<sup>1</sup> “Can burnt toast and roasted potatoes cause cancer?”,<sup>2</sup> and “Coffee: The science behind the health claims”<sup>3</sup> appear in the media daily. These articles are designed to engage, inform, or potentially shock a reader. Former editor of *New Scientist*, Michael Kenward, explains:

*Science writing is about explaining complex ideas that nobody wants to keep secret; science journalism is about explaining things that everyone can understand but that some might prefer to keep buried.<sup>4</sup>*

But what differentiates medical journalism from medical writing? Essential features are subject matter research and delivering understandable, impactful contents. Whereas medical writers produce text on topics defined by the client or institution that is primarily informative or intended for regulatory bodies, the priority for medical journalists is to narrate stories that will engage and maintain interest until the last paragraph. This involves delving into the context of what is being reported, seeking comments, speaking to independent experts, and highlighting both positive and negative aspects of the story.<sup>5</sup> According to Sonya Collins, the secret is to hook readers “with the stories of the real people affected by the science and painting verbal pictures of hard-to-grasp concept”.<sup>6</sup> This requires a high-level understanding of the science behind each piece. Her experiences as an independent journalist soon refuted her preconceptions that medical journalism “was dry, heartless and devoid of storytelling and poetry”.<sup>6</sup>

Target audiences are different: For medical journalists, it can range from healthcare professionals, providers, governing bodies to newspaper readers and television audiences. Thus, targeting the narrative is important. Some scientists and healthcare professions may not feel comfortable with such a popular approach or using

metaphors like describing the parts of a cell as resembling a fried egg. Sonya Collins defends this by quoting Professor Patricia Thomas, Programme Chair of the University of Georgia’s Master’s in Health and Medical Journalism course: “A good health story makes readers feel smart.”<sup>6</sup>

Both medical writers and journalists work under time pressure, but this can be particularly intense in the newspaper or broadcasting world. Here you may be asked to produce a story with just a few hours’ notice.<sup>7</sup> The temptation for the media is just to accept material already written by a press officer working on behalf of industry, government, or a lobbying group. Also, you are unlikely to become rich. While many are employed as editors or staff reporters by a media organisation, the competition is intense and companies are cutting back. Unless they have established work streams, freelancers often struggle to get published and face competition from unpaid armateurs.<sup>8</sup>

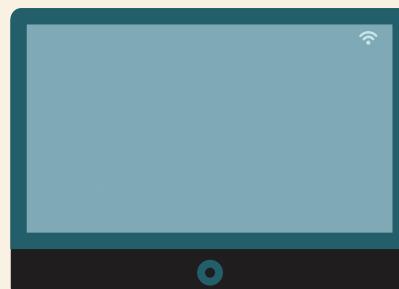
## What medical journalists say about their field: An interview with two senior journalists

To find out more about medical journalism, we interviewed two senior journalists with wide experience in medical journalism: Nigel Praities, editor at *Pulse* magazine, and Jacqui Wise, a freelance journalist who regularly writes for *The BMJ*. Between them, they have more than 35 years’ experience in medical journalism.

### How does medical journalism differ from medical writing?

**Nigel:** Medical journalism is more fast-paced. We must react to stories emerging minute-by-minute. There is a greater range of content too; as well as news, we also produce blogs, opinion pieces, webinars, advice articles, and opportunities for continued professional development.

**Jacqui:** I would probably use the terms “medical journalism” and “medical writing” interchangeably. I suppose medical journalism would involve getting



comments from experts, analysing information, or uncovering a new story. Medical writing is more summarising or exploring a topic.

#### **What are the usual channels through which medical journalism is disseminated today?**

**Nigel:** Through print, online, social media, word of mouth. There has been a revolution in recent years towards online and social – a very different model of communicating with your audience.

**Jacqui:** Newspapers, consumer magazines, scientific or professional journals, online journals, websites, and publications from public relations or pharmaceutical companies. There has been a shift towards more online content. A lot of magazines aimed at doctors no longer exist or only exist online, such as *GP* and *Doctor*.

#### **How do media channels differ?**

**Nigel:** I enjoy them all. There is nothing like holding a printed journal in your hands, but I also really enjoy the instant reaction and two-way conversations you can have online and through social media. I learn so much through interacting with readers – this is probably the area I enjoy the most.

**Jacqui:** I started work as a news reporter on *MIMS Magazine Weekly* – a clinical magazine for general practitioners (GPs) owned by Haymarket that closed down some years ago, I then moved to *Doctor* – a larger weekly newspaper for GPs that covered clinical and political news. I was first clinical editor and then news editor. This was enjoyable, as there was a large team of reporters and there was the pressure of daily deadlines. We had to compete with *GP* and *Pulse* to get the good stories and the best coverage of issues such as pay deals, the ARM (the British Medical Association's annual meeting), health reforms, and so on. *Doctor*, which was owned by Reed, has also since closed. I then moved to *The BMJ* as news editor. This was enjoyable in a different way – it was a more relaxed working environment in-house for the British Medical Association, and it was interesting working with doctors. At the time, there were no in-house journalists and so I commissioned freelance journalists from around the world to write most of the news stories. I left to have my first child and moved to South Africa for 6 years.

When I returned to the UK, I freelanced – working from home. I have written for many publications including *The Guardian*, *Bella*, *Top Sante*, *The BMJ*, *Lancet Infectious Diseases*, *WHO Bulletin*, and *Pharmaceutical Journal*, plus reports etc. for public relations companies.

#### **How does one find a story and validate its accuracy?**

**Nigel:** Depends on the story – if there is a source, we can go to and confirm, then this is easily done. Other times it is more complicated. You need multiple sources and to consider whether something is robust enough to put into the public domain.

**Jacqui:** Sometimes a news or features editor asks me to write on a subject and gives me a brief. Sometimes I come up with an idea and contact them. Nowadays, I mainly write for *The BMJ* for the news or features sections. The story will usually be based on a piece of new research, report, or event. I would only cover something that came from a reputable peer reviewed journal or established body. I would contact experts to check the validity of the story.

#### **Is there a demand for medical stories?**

**Nigel:** There is a huge interest in medical stories as it has an impact on everyone. A good story is one that gets picked up by the national media or TV news – this happens more often than you think.

**Jacqui:** I think demand is definitely decreasing.

#### **What are your most exciting pieces of work to date?**

**Nigel:** Very hard to choose, but we have campaigned for a number of years for additional support for struggling GPs and practices that are about to close. This lobbying has helped lead to a major support package from the National Health Service, and we have been praised for putting this on the national agenda.

**Jacqui:** I had a number of features published in *The Guardian* in the late 1990s and that was a thrill to see my name in a national newspaper. Sadly, their health section then

shrank, and I stopped writing for them.

I enjoyed writing a feature for *The BMJ* on a medical research scandal involving a German anaesthesiologist named Joachim Boldt. Almost 90 fraudulent studies of his were withdrawn after it was found he fabricated study data. It was a fascinating story to write. I also enjoyed interviewing the cancer patient and journalist Steve Hewlett for a *BMJ* "Medicine and the Media" feature. He was a lovely man who sadly died only weeks after talking to me.

#### **What advice would you give on starting a career in medical journalism?**

**Nigel:** My advice would be start writing and get it published – it does not matter what it is or where. I started out freelancing for *The Guardian*, simply pitching ideas to one of their editors. There are no fixed qualifications, although a journalism qualification is always helpful.

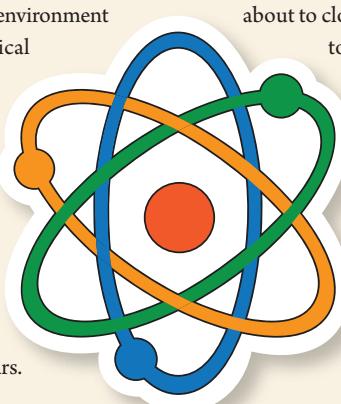
We run internship programmes here for new journalists, although competition is fierce.

**Jacqui:** You need a scientific background but not necessarily medicine – I have a biology degree. You also need to be able to write, obviously! You also need some sort of journalistic training. It's harder nowadays to get training on the job – the big newsrooms that used to exist for *Doctor*, *Pulse*, *GP*, and other publications are no longer there. This is a great shame as this was where most people learnt a lot.

#### **What about remuneration and other incentives?**

**Nigel:** No one does journalism for the money. There are lots of freelance opportunities, as many publications are understaffed, and this area is so complex.

**Jacqui:** No, I don't think it is that well paid. But it is flexible, and you can work from home a lot of the time. Payment depends on where it is published, the length, etc.: Roughly £120-£200 for a news story, £250-£500 for a feature. I travelled a bit while on *Doctor* to cover scientific conferences abroad, but that was when pharmaceutical companies would pay your costs. Some freelancers I know still get taken to conferences by pharmaceutical companies to write stories or conference reports. It can be stressful if you need to rely on journalism to pay your bills and you don't have a regular outlet for your work.



### What are the exciting and interesting aspects of medical journalism?

**Nigel:** You can make people laugh, cry, or feel angry, and perhaps occasionally, change their view of the world. That is an incredible power – but also a responsibility.

**Jacqui:** I enjoy working to deadlines; without one I would never get anything done. The work can be interesting – although it can be very boring at times. Getting your head around a complex topic and putting it across clearly can be very satisfying. Features involve a lot more work but are ultimately more satisfying than news. However, the good thing about writing a news story is that it can be “done and dusted” quickly, and then you can forget about it. I like the flexibility of working as a freelance journalist – great if you have kids and want to work from home.

### Making the transition from medical writing to medical journalism

If you are a medical writer looking to transition to medical journalism, your understanding of scientific writing will help, but you will need to be able to investigate and critically analyse and not only summarize or describe. While it is possible to be both a medical writer and a medical journalist, some may find switching between the different styles of writing challenging.<sup>5</sup>

As discussed, most commercial medical writing involves presenting data in the interests of companies and organisations, medical journalism requires the evaluation of numerous sources to deliver what should be a balanced and unbiased story. Unfortunately, articles such as the one on burnt toast seem more intent on worrying rather than informing the reader. In a 2005 article,<sup>9</sup> EMWA member Jo Whelan offers sensible advice on “true” journalism rather than uncritically accepting press releases or reproducing the work of others, a process nicknamed “churnalism” (Box 1).

Different sources tend to offer the same advice for budding medical journalists: Simply start writing, keep going, and reach out to a wide range of potential outlets. Researching the published content of journals, websites, and



### Box 1. Journalistic tips for investigating a story

In a 2005 article published in *The Write Stuff*,<sup>9</sup> Jo Whelan gives the following tips for investigating a story:

1. Never take press releases, corporate publications, or newspaper/magazine articles at face value.
2. Get the background on your story.
3. Ask searching questions when you interview people.
4. Always get an independent expert to comment.
5. Be aware of people's motivations, agendas, conflicting interests, and possible prejudices.
6. Don't report statements as fact. Use qualifying phrases like “according to Kuritech”, or “says Dr X”.

magazines is a good way of seeking inspiration. Approach companies using freelance writers, and submit original pieces or suggest new ideas. If you are unsuccessful, ask for feedback to improve future submissions. The websites for the

Association of British Science Writers ([www.absw.org.uk](http://www.absw.org.uk)) and the Medical Journalists Association ([www.mjauk.org](http://www.mjauk.org)) are excellent resources and are used by editors to source freelance journalists.<sup>5</sup>

Formal journalism qualifications and in-depth experience are an asset, but what matters more than anything is a good writing style, a desire to disseminate scientific stories, and the ability to learn quickly.<sup>10</sup> You must love words. Catherine Murray writes

“I love using words to reveal the pictures emerging from the fog of my sensations and I don't feel satisfied until I find the exact words which give shape to those pictures. And the more I am able to create a whole picture reflecting the complexity of reality, the happier I feel.”<sup>11</sup>

### Conclusion

Medical journalism demands an investigative nature, the ability to critically evaluate evidence and the ability to rapidly produce engaging pieces of wide interest. It is a stimulating, sometime fast-moving career, although often not a well-paid one. For those interested in medical journalism as a career, excellent writing skills and an ability to learn quickly are probably more important attributes than journalistic qualifications or deep knowledge.

We end by paraphrasing our two contributors:

*Medical journalism has the potential to change somebody's outlook on the world – with this opportunity comes great responsibility.*

### Acknowledgements

We are grateful to Jacqui Wise and Nigel Praities for their time and insight.

### Conflicts of interest

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

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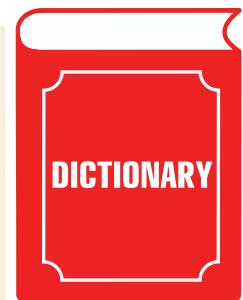
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A scenic view of Park Güell in Barcelona, Spain, featuring the iconic organic architecture of Antoni Gaudí. The image shows the winding paths, colorful ceramic tile mosaics, and the city skyline in the background under a clear blue sky.

**Save the date**

**The 46th EMWA Conference in  
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# News from the EMA

The articles included in this section are a selection from the European Medicines Agency's News and Press Release archive from July 2017 to September 2017. More information can be found on the Agency's website: [www.ema.europa.eu](http://www.ema.europa.eu)

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## EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans

**July 7, 2017** – The European Medicines Agency (EMA) has concluded its review of gadolinium contrast agents, confirming recommendations to restrict the use of some linear gadolinium agents used in MRI body scans and suspend the authorisations of others. The recommendations – confirmed by EMA's Committee for Medicinal Products for Human Use (CHMP) – follow a review that found that gadolinium deposition occurs in brain tissues following use of gadolinium contrast agents.

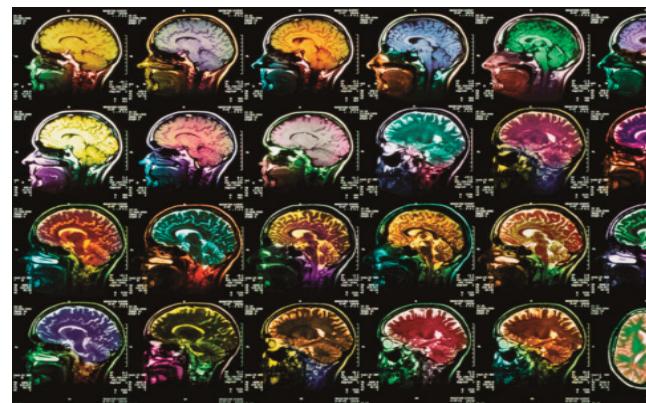
There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients; however EMA has recommended restrictions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition.

The intravenous linear agents gadoxetic acid and gadobenic acid can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need. In addition, gadopentetic acid given intra-articularly

(into the joint) can continue to be used for joint scans because the dose of gadolinium used for joint injections is very low.

All other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in the European Union (EU). Another class of gadolinium agents known as macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) are more stable and have a lower propensity to release gadolinium than linear agents. These products can continue to be used in their current indications but in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.

The suspensions or restrictions on linear agents can be lifted if the companies concerned



provide evidence of new benefits in an identified patient group that outweigh the risk of brain deposition or if the companies can modify their products so they do not release gadolinium significantly or cause its retention in tissues.

EMA's final recommendations will be sent to the European Commission (EC), which will issue a final legally binding decision applicable in all EU Member States.

## Revised guideline on first-in-human clinical trials: Strategies to identify and mitigate risks for trial participants

**July 25, 2017** – The EMA has revised its guidance on first-in-human clinical trials to further help stakeholders identify and mitigate risks for trial participants.

First-in-human trials are a key step in medicines development, where a medicine already tested in vitro, in animals or in other preclinical studies is administered to people for the first time. Participants in these trials, often healthy volunteers, face an element of risk as the ability of researchers to predict the effects of a new medicine on people is limited before it is actually studied in humans. Only on very rare occasions, however, have participants experienced serious harm.

The safety and well-being of trial participants should always be the utmost

priority when designing early clinical trials. The guideline puts emphasis on the sponsor's responsibility to define the uncertainty associated with the medicine tested at each step of the development and to describe how the potential risks that might arise from this uncertainty will be addressed within the design and conduct of the trial. The approach must be supported by a well-documented scientific rationale from the outset and be responsive to data emerging over the course of the trial itself.

The revision takes into account the fact that in the past 10 years trial protocols have become increasingly complex and now often include different parts within a single clinical trial protocol, aimed at assessing for example single and multiple ascending doses, food

interactions, or different age groups.

The strategies to mitigate and manage risks for trial participants described in the guideline refer specifically to the calculation of the starting dose to be used in humans, the subsequent dose escalations, and the criteria for maximum dose. Guidance is also provided on criteria to stop a study, the rolling review of emerging data with special reference to safety information for trial participants, and the handling of adverse events in relation to stopping rules and rules guiding progress to the next dosing level.

This guideline was revised in cooperation with the EC and the representatives of the Member States of the EU through the EU Clinical Trials Facilitation Group (CTFG).

## EU report: More evidence on link between antibiotic use and antibiotic resistance

**July 27, 2017** – A new report from the three agencies, the European Food Safety Authority, the European Medicines Agency, and the European Centre for Disease Prevention and Control, presents new data on antibiotic consumption and antibiotic resistance and reflects improved surveillance across Europe.

The Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report highlights that there are still important differences across the EU in the use of antibiotics in animals and humans. Overall antibiotic use is higher in food-producing animals than in humans, but the situation varies across countries and according to the antibiotics.

In particular, a class of antibiotics called polymyxins – which includes colistin – is used widely in the veterinary sector. It is also increasingly used in hospitals to treat multidrug-resistant infections. Other antibiotics are more often used in humans than in animals. These include third- and fourth-generation cephalosporins and quinolones, antibiotics that are also considered critically important for human health.

The report notes that resistance to quinolones, used to treat salmonellosis and campylobacteriosis in humans, is associated with use of antibiotics in animals. The use of third- and fourth-generation cephalosporins for the



treatment of infections

caused by *Escherichia coli* and other bacteria in humans is associated with resistance to these antibiotics in *E. coli* found in humans.

The conclusions are in line with those of the first report published in 2015. However, the

availability of better quality data allowed for a more sophisticated analysis. Experts of the three agencies recommend further research to better understand how the use of antibiotics and resistance affect one another.

## EMA encourages tailored development of medicines for older people

**August 1, 2017** – The EMA is inviting comments from the public by January 31, 2018, on a reflection paper on how medicine developers can better address the needs of older people who take medicines.

In general, older people are the highest users of medicines. According to Eurostat, they are expected to make up almost a third of all Europeans by 2050, and they take more medicines than the rest of the population. Yet, medicines are rarely developed or packaged to take into account their specific needs. For example, some older people can face challenges such as difficulty opening boxes or bottles, reading instructions, swallowing or breaking tablets and capsules, which can result in medicines not being taken as intended, medication errors, and

ultimately a reduced quality of life.

The reflection paper describes aspects that medicine developers may consider when designing medicines for older people, such as selecting appropriate routes of administration and dosage forms, dosing frequency, excipients, container closure systems, devices and technologies, and user instructions in the product information.

For example, when there is evidence that older people find it difficult to break a tablet by hand, companies may find ways to improve the

breakability of the tablet or consider alternative administration approaches, such as small tablets in a dose dispenser. Similarly, companies may consider redesigning the containers so that older patients can open them easily without any assistance.

Comments are particularly invited on the accuracy of tablet breaking, the administration of medicines through feeding tubes, and on multiple compliance aids and multiple drug dispensing systems (containers that clearly state the name of the day or the moment when a medicine needs to be administrated).

Depending on the outcome of the public consultation, the content of the reflection paper might be further developed into regulatory or scientific guidance.





**August 7, 2017** – The European Union Intellectual Property Office (EUIPO) has approved the registration of "EU PAS Register" as a European Union trade mark (EUTM). A EUTM grants exclusive rights in all current and future Member States of the EU and can be renewed every 10 years.

Launched in November 2010, the EU PAS Register is a unique source of information on the safety and effectiveness of authorised medicines. It is an openly accessible platform with infor-

## Platform for post-authorisation studies registered as EU trade mark

mation on observational post-authorisation research in medicines already marketed in Europe and includes study protocols, study results, related publications and other relevant information.

The information in the EU PAS Register helps to reduce publication bias through increased transparency of medicines research, improves the quality of post-authorisation studies by facilitating peer-review of protocols and results, promotes collaboration among stakeholders, and ensures compliance with EU pharmacovigilance legislation requirements.

By July 31, 2017, 1,145 studies had been registered on the platform. 583 (50.9%) have been requested by a regulatory authority, and 368 (32.1%) are finalised.

The trade mark, registered on July 10, 2017,

will reinforce the European Medicines Agency's (EMA) legal control over the name of the platform and its content. The EU PAS Register is now acknowledged internationally as a repository of observational post-authorisation studies. The use of the platform is widely recommended in scientific publications, guidelines, and textbooks. Although initially the main aim of the EU PAS Register was to collect studies conducted in the EU, researchers from outside the EU are also registering studies to increase transparency of their research.

The EU PAS Register was developed through the European Network of Centres for Pharmaco-epidemiology and Pharmacovigilance (ENCePP), which is coordinated by EMA to support research in pharmacoepidemiology and pharmacovigilance.

## New commitment allows FDA to share full inspection reports with EC and EMA

**August 23, 2017** – The European Commission (EC), the United States (US) Food and Drug Administration (FDA), and the EMA have signed a new confidentiality commitment that allows the US regulator to share non-public and commercially confidential information, including trade secret information relating to medicine inspections, with EU regulators. This confidentiality commitment is a milestone in the ongoing implementation of the mutual recogni-

tion of inspections of medicine manufacturers, and it aims to strengthen the EU-US relationship. Ultimately it will contribute to a more efficient use of inspection resources by regulators for the protection of human and animal health.

The EU and the US have had confidentiality arrangements in place since 2003, allowing for the exchange of confidential information as part of their regulatory and scientific processes. However, complete exchange of information was

not possible under these arrangements.

The new confidentiality commitment formally recognises that FDA's EU counterparts have the authority and demonstrated ability to protect the relevant information. This step now allows the sharing of full inspection reports, allowing regulators to make decisions based on findings in each other's inspection reports and to make better use of their inspection resources to focus on manufacturing sites of higher risk.

## Factor VIII medicines: No clear and consistent evidence of difference in risk of inhibitor development between classes

**September 9, 2017** – The EMA has concluded that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: Those derived from plasma and those made by recombinant DNA technology.

Factor VIII is needed for blood to clot normally and is lacking in patients with haemophilia A. Factor VIII medicines replace the missing factor VIII and help control and prevent bleeding. However the body may develop inhibitors as a reaction to these medicines, particularly when patients first start treatment. The inhibitors reduce the medicines' effect, so that bleeding is no longer controlled.

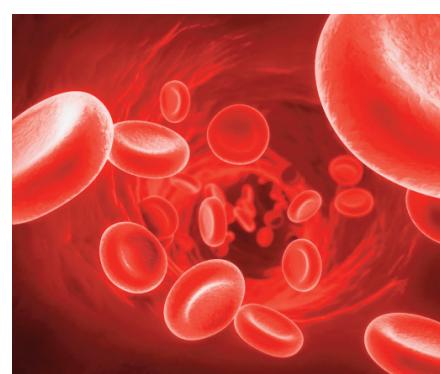
EMA looked at data to assess whether there is a difference in the risk of inhibitor development between factor VIII medicines manufactured with DNA technology and those

extracted from human blood. EMA concluded that there is no clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines. Patients should therefore continue to use their factor VIII medicines as prescribed by the doctor.

EMA's review was started following publication of the SIPPET study, which concluded that recombinant factor VIII medicines had a higher incidence of inhibitor development than plasma-derived medicines containing von Willebrand factor. The review concluded that the data did not show any statistically or clinically meaningful difference in inhibitor risk between factor VIII classes. The SIPPET study was designed to assess class effects and included a small number of factor VIII medicines, and the review considered that the results cannot be extrapolated to individual

medicines, especially since many were not included in the study. Therefore, the risk for each product will continue to be assessed as more evidence becomes available.

To reflect current knowledge, the prescribing information of factor VIII medicines will be updated to include, as appropriate, inhibitor development as a very common side effect in previously untreated patients, and as an uncommon side effect in previously treated patients. The warning on inhibitor development will be amended to state that low levels of inhibitors pose less risk of severe bleeding than high levels.



# Profile

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## An interview with Steven Walker

Founder, director, and co-owner of London- and Berlin-based medical communications agency Stgilesmedical



*As the sun beats down on another glorious London afternoon, you decide to take a step away from the hustle and bustle of the Oxford Street throngs, and into the leafy courtyard of St Giles-in-the-Fields Church. And, as you stroll past the cool shadow of the towering Palladian edifice, where the dappled sunlight dances between the leaves of the courtyard trees and glints off the stained-glass windows soaring above, you come to the historic Vestry House, built in 1733. Housed within its wood-panelled rooms is Stgilesmedical, a niche agency founded in 2014 by Yvonne Anderson and Steven Walker, and we've come here to hear his story.*

**MEW:** Hi Steven, thanks so much for agreeing to talk to us. First things first, how did you come to found a company in a vestry?

**(SW):** When Yvonne and I started our new company, calling it after St Giles seemed appropriate. He is the patron saint of cancer, mental health, disability, and epilepsy, all issues close to our heart. And, yes, we did want to be different. We needed a new office in central

London, so one day while sitting in the garden of St Giles-in-the-Fields Church, Covent Garden, I met the rector and cheekily asked whether he might have space available. After some reflection, he agreed to rent out his old office in the Vestry House. So now we are Stgilesmedical, St Giles-in-the-Fields Church, 60 St Giles High Street. It was meant to be!

**MEW:** In the past 15 years, you've founded two successful communications agencies, Bioscript and Stgilesmedical. What guidance would you give to an entrepreneur looking to found a small company in today's marketplace?

**(SW):** Well, firstly I'm flattered to be considered as having something worthwhile to say on the issue – it is difficult to judge how successful your business is when you are in the thick of running it! – but here are a few thoughts which might be helpful:

- It helps knowing what you want to achieve. You need to be single-minded and to believe that you can get there. A streak of madness is

also beneficial: life as an employee or a freelancer is much less stressful than being in charge!

- You need experience of the industry, some money behind you and at least one project to start off with. Be prepared to work all hours, worry about stuff in between times, and pay your team but not yourself.
- I've found it invaluable to have an energetic business partner with complementary skills, to provide support when you are lost or flagging.
- Never miss an opportunity. Build a network of useful contacts and reach out to them regularly. Projects usually come from contacts rather than marketing, and doing a good job often brings more work. So far, none of the many emails I have sent to procurement teams and publication managers have ever brought anything of value.
- Finding the right staff is extremely difficult. When you start out, you may need to hire a team of less experienced colleagues and develop them yourself, rather than hiring in experts from Day 1. Don't underestimate the time and energy this requires, and be prepared to cope with unexpected time off and personal crises.
- Get your name known by writing articles, attending meetings, and supporting educational activities. EMWA and ISMPP meetings are a great way to network and raise your profile.
- Graham Shelton of Oxford PharmaGenesis gave me the following pieces of advice: "Follow the money" and "Listen to the business". By these, I think he meant to seek out projects where there is current need or investment, be prepared to adapt as circumstances change, and avoid pushing in one direction when circumstances are taking you somewhere else.
- Oh, and most importantly, make some time for yourself and your family, and have some fun with your team along the way!

**MEW:** You describe Stgilesmedical as a “niche” agency – others use the term “boutique” agency. What do you see as the advantages of and disadvantages of managing a smaller agency?

**(SW):** I think that we are more “niche” because our team of medics, scientists, writers, educators, and patient representatives understand the needs of industry as well as healthcare professionals and those on the receiving end. We are great at delivering unusual and challenging projects and working alongside our clients to share their load. Supporting good medicine is what drives us. All of this you can do if you are small and privately-owned; once accountants, marketers, and multiple account directors become involved then the ethos changes.

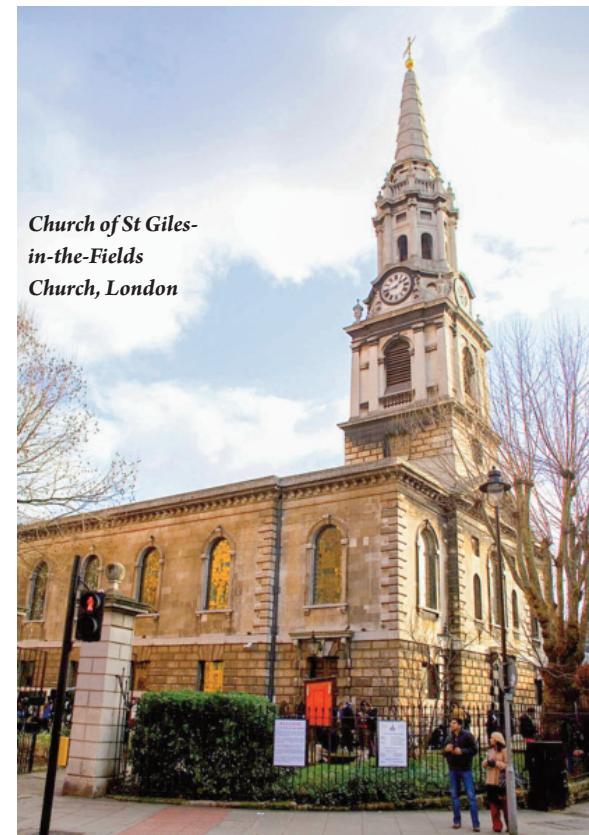
**MEW:** Tell us a bit about what you've been up to recently.

**(SW):** 2017 has been a mad year. I have never worked so hard or felt so satisfied by what we have achieved. It all started with our successful ‘Learning Room’ session for new members of the profession at the ISMPP European meeting in London. Then there was *Bionnale* in Berlin, followed by the Expert Symposium at EMWA in Birmingham. We have also run three educational MedComms events in Germany.

Several projects have proven challenging: for example, making sense of a European multicentre cardiovascular project, supporting a paper on behalf of the German Interdisciplinary Association for Intensive Care and Emergency Medicine, and delivering a series of CSRs reporting the early results of an exciting orphan drug. A new area for us is proving to be medical devices and aesthetics.

On a lighter note, Giles the Mouse, our company mascot, has just completed a week-long, 2,000-mile trip for Hospice UK. He travelled from Nordkapp in the very north of Norway to Bergen in the south, accompanied by myself and my colleague, Tony Docker. There is more about our adventures at [www.stgmed.com/giles-goes-to-norway](http://www.stgmed.com/giles-goes-to-norway).

**MEW:** A mouse hopping across the fjords! I'm sure that there are plenty of our readers who'd love to do something charitable and altruistic like that – how



*Church of St Giles-in-the-Fields  
Church, London*

Photo by Prioryman, is licensed under CC BY-SA 4.0.  
The image is available at: [https://en.wikipedia.org/wiki/St\\_Giles\\_in\\_the\\_Fields#/media/File:St\\_Giles\\_in\\_the\\_Fields\\_January\\_2012.jpg](https://en.wikipedia.org/wiki/St_Giles_in_the_Fields#/media/File:St_Giles_in_the_Fields_January_2012.jpg).

**can others in the industry make a positive contribution like you've managed to?**

**(SW):** Just do it! Having our own business allows us to do quirky things for no or very little money. These have included supporting the MSc in Scientific Communication course at Manchester Metropolitan University and working with one of our new medical schools on a programme to develop reflection, resilience, and mindfulness. We're also particularly proud of our research project in support of Hospice UK which looks at ways to reduce unnecessary hospital admissions at the end of life. Our visits to numerous units around England have gone well, while analysing and writing up the mass of quantitative and qualitative data is proving a challenge.

Events are also a good way to raise awareness for a particular issue. A few months ago, we supported the “Art of being a patient” exhibition, where Tony Pickering – who is an artist, a patient, and a carer – talked us through his powerful images and artwork, accompanied by jazz, champagne, and canapes. See [www.stgmed.com/tony-pickering](http://www.stgmed.com/tony-pickering) for more details.

**MEW:** You also recently registered Stgilesmedical GmbH, and are opening up offices in Berlin. What led you to

**develop a presence in Germany?**

**(SW):** Our new Berlin office was opened on 1st October at the Charlottenburg Innovation Center, with a small team from Germany and the UK. I will be travelling between our two offices. The reasons behind this move are Brexit, a personal connection with Germany, and the fact that many of our clients are based in the DACH countries (Germany, Austria, and Switzerland) so our being on-site will help us to look after them better.

**MEW:** What impact, if any, do you think Brexit might have on British healthcare agencies with European offices?

**(SW):** Only time will tell. I am sure agencies in the UK will continue to survive, especially as staff costs here are generally lower. On the other hand, when faced with two similar choices, it is human nature for a European client to choose the more local supplier.

**And finally, some quick-fire questions:**

**Theatre or boxset?**

Theatre

**Cook or be cooked for?**

Cook

**Early start or late finish?**

Late finish – I am not good first thing in the morning.

**Classic rock or classical baroque?**

I like all music except country. Highlights for this year are regular attendance at Holland Park Opera, the Camden Rock Festival, Lollapalooza Berlin, and working as a steward at Weyfest.

**English bitter or German pilsner?**

German wheat beer with a slice of lemon, whilst listening to loud music in the summer, and a pint of real ale by the fire in an English country pub in the winter.

## Contact Information

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# Getting Your Foot in the Door

## On internships, scribes, and work experience



For this edition of GYFD, I would like to provide some background information about internships, including the history of the term and answers to some frequently asked questions about it. The objective is to provide a better overview of internship that goes beyond preconceptions based on White House scandals, college students' nightmares, and reality TV.

### How did internships originate?

I am delighted to report that *internship* has a very honourable history. It has close ties to Europe, and the term itself is linked to medicine. According to some, internships can trace their roots to the European apprenticeship system in the Middle Ages.<sup>1,2</sup> The term *apprenticeship* meant "to bind to a master for instruction in his craft" in the 1630s.<sup>3</sup> Under this system, children as young as 11 would start vocational training under a master craftsman to learn a trade. Skills and know-how during this time were transferred to the apprentice by shadowing the master. At the end of about seven

years, the apprentice should be fully qualified to practise the profession he or she trained for. Nowadays, the apprenticeship system,

The term "internship" has a very honourable history. It has close ties to Europe and is linked to medicine.

though of shorter duration, is still very much practised in Europe, strictly regulated by labour and education authorities.<sup>1,2</sup>

The term *intern* comes from the French word *interne* which means "assistant doctor."<sup>3</sup> It was supposedly coined during World War I to refer to someone who has a medical degree but does not have the licence to practise medicine.<sup>1</sup> During internship, the intern gets hands-on training in the field of medicine under the supervision of a licensed practitioner and eventually becomes a fully trained, qualified physician. Today, the same qualification pathway exists in many countries as medical doctors go from internship to residency before obtaining a full attending position.

I personally think – though I am no historian – that internships or apprenticeships go back even earlier. What comes to my mind are the scribes of ancient Egypt. These highly trained professionals were sent to a special school at an early age to learn reading and writing of hieroglyphs under a master scribe. At the end of many years of training,

scribes took on a highly specialised profession in a predominantly illiterate society.<sup>5</sup> It was always thought that only boys

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were qualified to become scribes. However, there are records of female scribes who had to achieve literacy to practise their professions as priests or as physicians. Even in ancient Egypt, doctors, male or female, had to be able to read medical documents.<sup>5,6</sup>

### What is the purpose of modern internships?

Nowadays, the term *internship* covers all forms of professional careers that require high level of qualifications<sup>4</sup> and the journey to full qualifications is not as Hogwarts-like as it used to be. In addition to internship and apprenticeship, the terms *traineeship*, *volunteership*, *placement*, and *job shadowing* are interchangeably used when referring to on-the-job training programmes that last for a few months. The distinctions between these terms are not very clearly defined and vary from company to company, from country to country. However, regardless of the term used, it is clear that there are two main purposes for this type of training activity:<sup>1,2</sup>

**To get a leg up:** One gains work experience that can pave the way to an entry level position.

**To get to test drive:** From the intern's perspective, one gets to try out one's hand in a certain field if one is not sure of the career path to take. From the company perspective, one gets to check out the "job fit" before making a job offer.

### Does an intern get paid?

In the old European system, apprentices lived with their masters and in many cases worked for their board and keep. Nowadays, the monetary conditions vary a lot and we often come across the terms "paid" and "unpaid" internships. Again the rules governing compensation would depend on the company and the country labour legislations. In the UK, the British government provides very useful guidance for both interns and institutions on this matter on their website.<sup>4</sup>

### Is internship considered work experience even if it is unpaid?

The term *work experience* generally refers to a period of time that a person spends in a company,

business, or institution outside the classroom environment. Regardless of the compensation arrangements, it is assumed that the intern learns something about working life in general and specific aspects of a profession. It is only appropriate that interns can put this activity down in their resumé/CV as part of their work experience. However, internships, especially unpaid ones, would not necessarily qualify as employment, hence, may not be listed under employment history.

## What are the qualifications required for a medical writing internship and how does it work?

In previous editions of the GYFD, we had two medical communications agencies<sup>7,8</sup> share with us information on their internship programmes. I still have to find a pharmaceutical company who can provide information about their medical

There are two main purposes to internship: To get a leg up and to get to test drive.

writing internships. Recently, I came across an advertisement for a regulatory writing internship position for a big pharmaceutical company. With

permission from the company, I am sharing an excerpt of the job advertisement in Box 1 below, though the role has already been filled. This job posting gives us a peek into the world of regulatory writing internships.

### Closing remarks

Does your company have an internship programme? Have you done an internship yourself? We'd love to hear from you. Please share your experiences with the GYFD community.

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#### **Box 1. Excerpt from an internship advertisement**

"This [internship] position offers candidates with a scientific background at an undergraduate/recently graduated level exposure to a key role within clinical drug development... Successful applicants will provide support to experienced associates... In order to get as broad an experience as possible, you will work with multiple associates... on a variety of different... projects. You will also have opportunities to interact with colleagues in [other countries] as well as [job] shadow members of the team. Along with providing project management, support, writing parts of documents, and liaising with key team members, you will start to develop important transferrable skills, including effective communication and negotiation, time management, problem solving, and matrix team working. Training and 1:1 coaching will be provided."

Required qualifications and skills are "good English written skills, developed interpersonal skills and a positive work ethic... and life science, physical science or clinical background."

### Acknowledgements

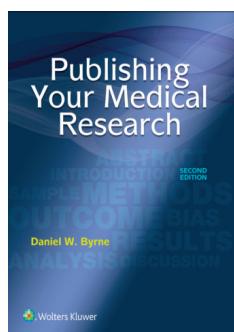
GYFD would like to thank Joyce Salita and Derek Ho for copyediting.

# Save the date

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

For more information: <http://www.emwa.org/Conferences/Future-Conferences/>

# In the Bookstores



## Publishing Your Medical Research (Second Edition)

Daniel W. Byrne

Wolters Kluwer, 2017

ISBN-13: 978-1496353863 (paperback)

ISBN-10: 1496353862

£44.40. 318 pages.

Daniel Byrne has taught courses on biostatistics and medical writing at Vanderbilt University since 1999. He wrote the first edition of *Publishing Your Medical Research* in 1998 to provide clinicians with practical information and advice on how to write a publishable paper. The second edition has the same general aims and consists of 34 chapters divided into five main sections: Planning, Observing, Writing, Editing, and Revising.

The Planning section (Chapters 2 to 12) focuses on tips and advice for designing and running clinical studies. The rationale is that journal editors and reviewers are looking for best practice in how trials are conducted and written up – and this is best addressed by not designing flaws into the research. I was tempted to skim through these chapters as not being very interesting to medical writers, but I'm glad that I didn't. As a freelance medical writer, I don't have any influence on the design of clinical studies but the finer points of trial design and how a flawed study design can be avoided, is good background information to understand. The chapters are meticulously written and include some useful and interesting tables. I particularly liked the panels containing the personal views of journal reviewers on what constitutes a "good" or "bad" paper.

The Observing section deals with the collection and analysis of data. I am no statistician and approached the chapters on statistical tests (Chapters 15 to 19) with some trepidation. I was pleasantly surprised (and relieved): these chapters are quite short, easy to follow, and informative. I now have a better understanding of some of the issues that investigators and study statisticians find so frustrating when discussing how the results of a trial should (or can) be presented. These chapters provide information on which statistical tests should

I wholeheartedly agree with Byrne's comments on clarity and readability and with his advice concerning internal peer review of the paper.

be used in particular circumstances and which are not appropriate, together with the reasons why. Chapter 19 considers multivariate analysis: this chapter is more detailed and explains how this form of analysis can be used to control for confounding factors in clinical trials. For this reason, selecting multivariate analysis alongside univariate analysis can enhance research papers. Byrne also points out that as statistics is a subject that is evolving and developing, investigators must ensure that they are using up-to-date statistical methodology.

Chapters 20 to 27 focus on writing the paper, with separate chapters devoted to the preparation of the title page, abstract, introduction, methods, results, discussion, and references. As in the early chapters, Byrne provides examples of feedback from reviewers and editors to highlight potential weaknesses in writing. Chapter 24 (Results) provides more guidance on presenting statistical results and advice on presenting clear and concise figures and tables. There is some excellent advice in Chapter 25 on how to set out the discussion. I particularly liked the list of eight questions that Byrne suggests should be answered in the course of the discussion – from pointing out the novelty in the research, to discussing the strength of the data set, the rationale for the choice of analysis, and how and why the findings might alter clinical practice.

While I agree with most of what Byrne has written in Chapters 20 to 27, I found some areas that were less satisfactory. While the meticulous attention to detail was a strength of the early chapters, here the level of detail in some chapters

just seems to add to their length without providing correspondingly greater insight. This is particularly true when the author reiterates information usually covered in a journal's instructions to authors. The need to check that the manuscript complies with the journal guidelines

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prior to submission is highlighted in a later chapter and means that this level of detail is unnecessary here. Personally, I did not find Tables 24.1 and 24.2 (providing preferred "terms" for pejorative or problematic "terms" for patients) helpful: Byrne covers the most important advice about describing patients and their disease in the text of Chapter 24, and I would have preferred it to have been left at that.

Byrne has included the International Committee of Medical Journal Editors' (ICMJE's) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals in Appendix A, and I think that he needs to reflect on whether the advice he gives about authorship in Chapter 20 (Title Page) is entirely in line with ICMJE recommendations. The absence of any mention of good publication practice (GPP) guidelines in Chapter 27 (Industry Publications) is, I feel, a major flaw. Although clinicians – the target audience for this book – were not the primary focus for the original GPP guidelines, in my opinion, Chapter 27 is inadequate in its current form and should be revised in future editions to include information on GPP.

I did not think that a separate chapter on references (Chapter 26) was necessary. Byrne provides good advice in this chapter, but for me this is so integral to the writing process that it should have been included in Chapter 22 (Introduction).

The Editing section (Chapters 28 to 31) focusses on final preparations for submission of the manuscript. I wholeheartedly agree with Byrne's comments on clarity and readability and with his advice concerning internal peer review of the paper. The checklist for internal review produced by Vanderbilt University that he reproduces in Appendix B is very interesting, and I can certainly see its usefulness in editing and subsequently revising a first draft. Table 30.1 – advice from editors and reviewers on how to improve writing style for impact – is also very useful and to the point, but I was not convinced

of the value of many of the other tables in this chapter (14 tables in total). A particular criticism is that Byrne has not taken sufficient account of differences between UK and US English in all of his suggestions.

The final section (Revising) is very short. Chapter 32 covers proofreading and layout: the advice is all good and the tables and figures are informative, but there is overlap with the writing section. Chapter 33 gives advice on writing a persuasive cover letter – once again, Byrne includes feedback from journal editors to add weight to his guidance. He also reiterates advice from journal editors to make a presubmission enquiry to ascertain the journal's interest in publishing a particular paper. Chapter 34 contains useful advice on responding to reviewers' comments as well as insight about the peer review process and how the decision to publish is made.

The book includes two further appendices (Appendix C provides a sample data collection form and Appendix D is a copy of the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects), a bibliography, and an index.

This book covers a vast amount of material in relatively few pages, although (as I mentioned earlier) some detail could be removed from some chapters. I would also question the idea of having more than 250 principles in a book designed to help people through an extended and complex process: Readers can't possibly hold all of these in their heads to prompt their next action, and I would suggest using numbered subsections instead.

The book is not intended for professional medical writers and editors, and, in my opinion, it is not a book that this group needs to read from front to back. Nevertheless, the Planning and Observing sections may be of interest to people without a background in clinical trials, and the Writing, Editing, and Revising sections could provide a gentle introduction for new medical writers and editors. For these reasons, medical writing departments in pharmaceutical companies and contract research organisations, as well as medical communications companies, may benefit from keeping a copy on their bookshelves.

#### Reviewed by

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# Journal Watch

Journal Watch is based on the French-language blog *Rédaction Médicale et Scientifique* by Hervé Maisonneuve available at [www.redactionmedicale.fr](http://www.redactionmedicale.fr).

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## "The highest (but also greatest) variability in the prevalence of spin was present in trials."

"In the scientific literature, spin refers to reporting practices that distort the interpretation of results and mislead readers so that results are viewed in a more favourable light." The above title and first sentence are from a systematic review that aimed to study the nature and prevalence of spin in the medical literature. Thirty-five reports, which investigated spin in clinical trials, observational studies, diagnostic accuracy studies, systematic reviews, and meta-analyses, were included. This systematic review was well conducted by a known Australian team.

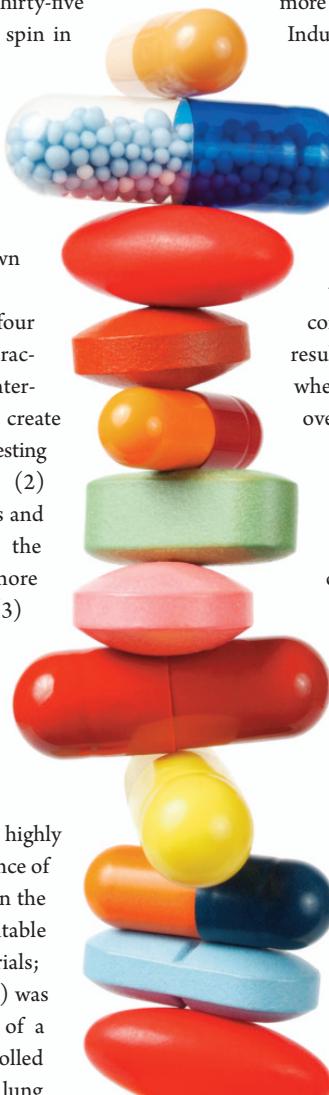
Spin was classified in four categories: (1) reporting practices that distort the interpretation of results and create misleading conclusions, suggesting a more favourable result; (2) discordance between results and their interpretation, with the interpretation being more favourable than the results; (3) attribution of causality when study design does not allow for it; and (4) overinterpretation or inappropriate extrapolation of results.

The prevalence of spin is highly variable. The highest prevalence of spin (100%) was observed in the main text of 10 implantable cardioverter defibrillator trials; the lowest prevalence (9.7%) was measured in the abstracts of a sample of randomized controlled trials of systemic therapy in lung

cancer. Nineteen of the 35 reports investigated the practices that researchers used to spin results. Four categories of spin practices were identified: inappropriate interpretation given study design; inappropriate extrapolations or recommendations for clinical practice; selective reporting; more robust or favourable data presentation. Industry sponsorship was not significantly associated with spin.

Further research is needed to better identify and classify spin; we don't know the impact of spin on decision-making.

Peer reviewers and journal editors should check to make sure that abstract and manuscript conclusions are consistent with the study results, that causal language is used only when appropriate, and that results are not overgeneralised. Clinical practice guidelines should be developed based on systematic reviews to ensure that recommendations are founded on rigorous data and not misleading conclusions. Structural reforms within academia are needed to change research incentives and reward structures that emphasise "positive" conclusions, including the pressure to publish and media attention.



## Reference:

Chiu K, Grundy Q, Bero L. 'Spin' in published biomedical literature: A methodological systematic review. PLoS Biol. 15(9):e2002173.

## Professional medical writing support was not associated with increased overall adherence to CONSORT for abstracts



A research note published in *F1000Research* analysed 463 abstracts from randomised controlled trials published between 2011 and 2014 in five journals (*New England Journal of Medicine*, *Annals of Internal Medicine*, *The*

*Lancet*, *The BMJ*, and *JAMA*). Acknowledged professional medical writing was observed in 66 articles (14.3%). The mean proportion of adherence to CONSORT for abstracts items reported in articles with (n = 66) and without (n

= 397) professional medical writing support was 64.3% versus 66.5%. Professional medical writing was associated with lower adherence to reporting study setting and higher adherence to disclosing harms/side effects and funding source. These data may not be generalisable to the biomedical literature as a whole. Although GPP3 (Good Publication Practice guideline) encourages transparency of medical writing support, it remains possible that it was not consistently acknowledged in the studied dataset.

### Reference:

Mills I, Sheard C, Hays M, Douglas K, Winchester CC, Gattrell WT. Professional medical writing support and the reporting quality of randomized controlled trial abstracts among high-impact general medical journals [version 2; referees: 2 approved]. *F1000Research*. 2017;6:1489.  
doi: 10.12688/f1000research.12268.2.

## The number of authors per article and the proportion of authors who contributed equally increased over time

A poster presented at the 8th International Congress on Peer Review and Scientific Publication (Chicago, September 2017) by two *JAMA* editors analysed papers published in 2005, 2010, and 2015 in *JAMA*, *Lancet*, and *New England Journal of Medicine*. The increase over time in the number of authors per paper has been steady (Table 1). The proportion of articles with group authorship increased significantly over time for *JAMA*, but not for *Lancet* or *NEJM*.

Although limited to three journals and to 10 years, these findings are consistent with previous studies focused on earlier periods and specialty



Table 1. Number of authors per paper in prominent medical journals

	2005	2010	2015	P Value for trend
<b>Authors per article, median (interquartile range)</b>				
JAMA	8 (5-11)	8 (6-12)	11 (7-18)	< 0.01
Lancet	9 (7-13)	12 (8-18)	15 (10-21)	< 0.01
NEJM	11 (7-15)	13 (9-20)	18 (12-26)	< 0.01

### Articles with authors who contributed equally, number/total (%)

JAMA	7/230 (3.0)	13/188 (6.9)	17/159 (10.7)	0.02
Lancet	9/172 (5.2)	16/165 (9.7)	31/178 (17.4)	< 0.01
NEJM	22/223 (9.9)	25/222 (11.3)	64/235 (27.2)	< 0.01

journals. Do major medical journals reflect the trend to increase collaboration between research teams?

### Reference:

Muth CC, Golub RM. Trends in authorship and team science in major medical journals, 2005–2015. International Congress on Peer Review and Scientific Publication. Chicago, September 2017.  
<http://peerreviewcongress.org/prc17-0167>.

## The relationship between physicians and the pharmaceutical industry: A heated debate for many decades

This well-conducted systematic review aimed to explore interactions between physicians and the pharmaceutical industry. Databases were searched and studies published between 1992 and August 2016 were obtained; 49 studies were included after authors screened 2170 articles; 2 reviewers independently extracted the data; 27 of the 49 studies were from the USA. The authors observed that pharmaceutical industry and pharmaceutical sales representative (PSR) interactions influence physicians' attitudes and their prescribing behaviour and increase the number of formulary addition requests for the company's drug.

The study results were classified in nine domains:

### 1. Extent of interactions between physicians and the pharmaceutical industry.

Such interactions are regular feature in the daily lives of physicians across the world.

### 2. Perspectives of physicians towards PSR interactions.

Physicians have a positive attitude towards PSR; information provided by PSRs, industry-sponsored conferences are important instruments to enhance the scientific knowledge.



### 3. Gifts.

Most physicians considered themselves immune to the influence of gifts.

### 4. Drug samples.

Accepting drugs led to higher branded drug prescription rather than generic prescribing.

### 5. Pharmaceutical representative speakers.

### 6. Honoraria and research funding.

### 7. Conference travel.

### 8. Industry-paid lunches.

Clerks, interns, and junior residents attended more company-sponsored lunches than senior residents.

### 9. Continuing medical education sponsorships.

Further studies are needed to evaluate the impact of these interactions with physicians over time and the benefits of various programmes on the clinical and ethical behaviour of the physicians.

### Reference:

Fickweiler F, Fickweiler W, Urbach E. Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians' attitudes and prescribing habits: a systematic review. *BMJ Open*. 2017;7:e016408. doi: 10.1136/bmjopen-2017-016408.

## Lack of time was the main barrier to publication for Paris-based health care researchers

A survey aimed to assess the difficulties experienced by researchers in the AP-HP (Assistance Publique – Hôpitaux de Paris, France), the largest public health institution in Europe, with more than 9,000 articles per year in PubMed-referenced journals. A 39-item electronic questionnaire based on qualitative interviews was sent by email to 7,766 researchers between May 28 and June 15, 2015.

The questionnaire was anonymously completed by 1,191 researchers (<45 years of age: 63%; women: 55%; physician: 81%; with PhD: 45%); 94% of respondents had published at least one article in the previous 2 years; 76% of respondents felt they were not publishing enough, mainly because of lack of time to write (79%) or

submit (27%), limited skills in English (40%) or in writing (32%), and difficulty in starting to write (35%); 87% of respondents would accept technical support, especially in English editing (79%), critical editing (63%), formatting (52%), and/or writing (41%), to save time (92%) and

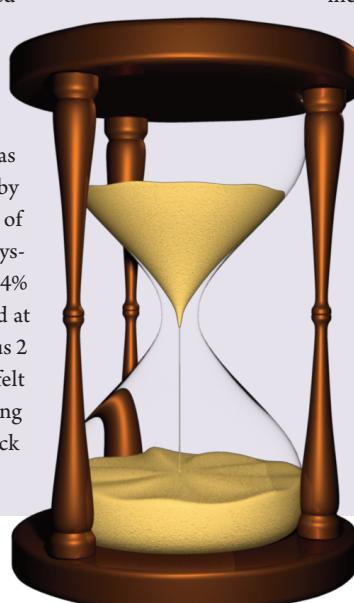
increase submissions to high impact factor journals and acceptance (75%); 79% of respondents would appreciate funding support for their future publications, for English editing (56%), medical writing (21%), or publication fees (38%). They considered that this funding support could be covered by AP-HP (73%) and/or by the added financial value obtained by their department from previous publications (56%).

It appeared that there was

a lack of knowledge of the job of medical writers and a confusion between the jobs of translator and medical writers. Indeed, English editing, critical editing, formatting/submitting, and writing were the main tasks for which support was needed, and medical writers fulfil all these functions. A lack of funding and a poor writing culture could explain this situation. French universities and/or research centres should have an academic/ scientific writing centre.

### Reference:

Duracinsky M, Lalanne C, Rous L, Dara AF, Baudoin L, Pellet C et al. Barriers to publishing in biomedical journals perceived by a sample of French researchers: results of the DIAzePAM study. *BMC Med Res Methodol*. 2017;17:96. doi: 10.1186/s12874-017-0371-z.





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## **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.



# The Webscout

## Preclinical studies – is animal testing necessary?

The drug regulatory authorities require testing in animals, to be exact in at least two mammalian species, before the first-in-human trials can be approved. Common criticism is that the results from animal studies can merely be extrapolated to humans and are therefore an unnecessary cruelty. How valid are the results indeed, and what could be an alternative to animal testing? The following websites and documents comment on these issues.

### <http://animal-testing.procon.org>

The website gives an overview on the history of animal experiments and the debate on it. Did you know that animal experiments can be dated back to ancient Greek and Roman scientists? Since then, animals have been used to experiment for the sake of mankind. Criticism of animal experiments also emerged in former centuries. Queen Victoria opposed animal testing in England. Her mindset towards animal testing strengthened the anti-vivisection campaigns, resulting in the first laws controlling animal experiments; Great Britain's Cruelty to Animals Act went into effect in 1876. The website also provides a detailed comparison of the pros and cons on this issue. The pro side argues that animal testing contributes to medical progress and that alternative testing systems are inadequate. The con side argues that animal testing is cruel and inhumane. According to the opponents, alternative methods are already in place that could replace animal testing. If you watch the debate show on the big question of "Is animal testing justified?" on YouTube ([www.youtube.com/watch?v=bD51eAOPSKc](https://www.youtube.com/watch?v=bD51eAOPSKc)), you will also get a full picture of pros and cons and an impression on the emotionality of the discussion on animal experiments.

### [www.piscltd.org.uk/ scipubs](http://www.piscltd.org.uk/scipubs)

The PETA International Science Consortium (PISC) addresses issues related to the replacement of animal experiments by alternative techniques. They provide a list of publications

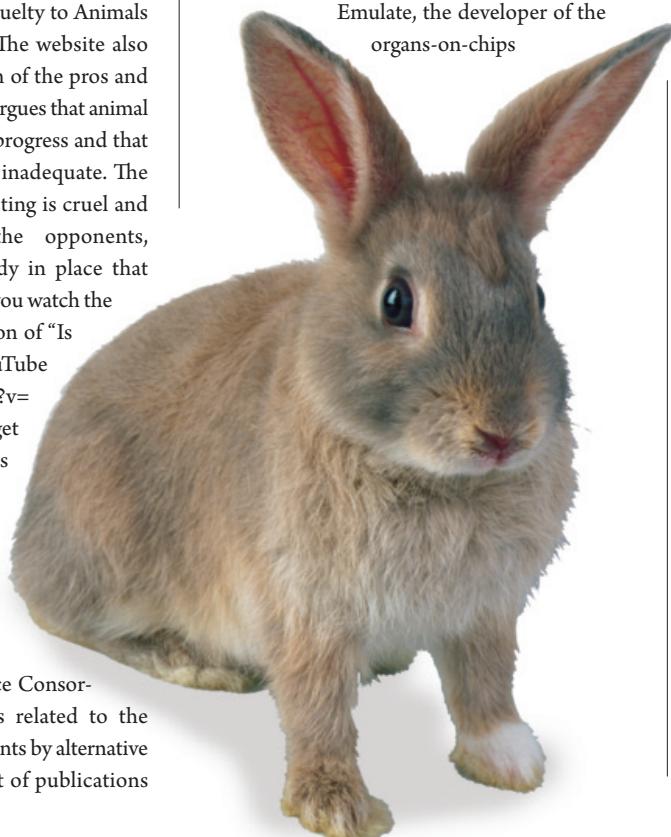
and posters on the applicability of animal study results to humans and on alternative testing procedures for pharmacological development and food and cosmetic safety.

### [www.piscltd.org.uk/alternatives-approved-by-regulators/](http://www.piscltd.org.uk/alternatives-approved-by-regulators/)

Some alternatives to animal testing have already gained approval. These include tests for eye irritation, skin irritation, and skin sensitisation, to name but a few. A detailed list and factsheets can be downloaded from the PISC website. For example, according to the European Pharmacopeia, a monocyte activation test can now be used in place of the rabbit pyrogen test for assessing pyrogenicity. The new test measures cytokine levels after exposure of human blood to the test substance.

### [http://emulatebio.com/insight/ functionality](http://emulatebio.com/insight/functionality)

It was only recently that the US FDA announced a collaborative research agreement with Emulate, the developer of the organs-on-chips



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technology. This technology uses micro-engineered living human cells to simulate human organs and can be used instead of animals in drug testing. According to Emulate, the system can predict the human response with greater precision and control than today's cell culture or animal-based testing methods.

### [http://ec.europa.eu/growth/ sectors/chemicals/epaa](http://ec.europa.eu/growth/sectors/chemicals/epaa)

The European Partnership for Alternative Approaches to Animal Testing is a collaboration between the European Commission, European trade associations, and companies from seven different industries including the pharmaceutical industry. Its aim is the replacement, reduction, and refinement (the so-called "3Rs") of animal experiments in regulatory testing. Currently, the project groups focus on eight topics. One of these is the Vaccines Consistency Approach Project: Vaccine quality control includes batch testing for safety based on animal tests as per legislation. The vaccines consistency approach strives to implement the 3Rs in vaccine manufacturing by strictly applying quality systems that ensure batch consistency.

### [www.aerzte-gegen-tierversuche.de/ agt-en/](http://www.aerzte-gegen-tierversuche.de/agt-en/)

Doctors Against Animal Experiments Germany (Ärzte gegen Tierversuche) is an association founded in 1979 that opposes animal experiments because of ethical, medical, and scientific reasons. They provide well-researched information for doctors, scientists, and the public. They also collaborate with international organizations such as the European Coalition to End Animal Experiments (ECEAE; [www.eceae.org](http://www.eceae.org)) to be heard on an EU legislator level. A film by the association ([www.youtube.com/watch?v=Mo25wUKNySg](https://www.youtube.com/watch?v=Mo25wUKNySg)) explains the organisation's viewpoint that animal experiments are ethically and scientifically questionable.

*Did you like this Webscout article? Do you have any questions or suggestions? Please feel free to get in touch and share your thoughts.*

# Good Writing Practice

## Inter-sentence discontinuity 1

### Omission



### Introduction

Conceptual component omission is a distraction to a content expert who expects specific argumentative conceptual components in the various sections of a journal article. As evidence, some of the components have become standardised in structured abstracts of many journals. In a structured abstract, the conceptual components are listed as subheadings, ensuring that the components are addressed. In a section of a journal article (e.g., Introduction) omission of an anticipated conceptual component (e.g., research problem) is more distracting than its misplacement into another section. However, both convey a nonprofessional tone.

In this first of two articles on inter-sentence discontinuity, we look at two examples of omitted conceptual components: Part 1, Research

Problem; Part 2, Hypothesis Justification, both of which are anticipated in an Introduction section.

### Part 1 – Research Problem Omission

#### *Example: Introduction section*

*Weight-bearing is one neuro-developmental treatment (NDT) principle usually applied by therapists before or in preparation for a functional activity. This treatment has been based on the assumption that weight-bearing facilitates development of muscle tone. Consequently, the purpose of this current study was to determine the effect of weight-bearing on hand-opening in children with cerebral palsy.*

In this example, the first sentence describes the pertinent research problem background; the

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second, the research problem; and the third, the research objective. However, the research problem is not stated.

### Revision

*Weight-bearing is one neuro-developmental treatment (NDT) principle usually applied by therapists before or in preparation for a functional activity. This treatment has been based on the assumption that weight-bearing facilitates development of muscle tone. However, no systematic study justifying this assumption has been reported. Consequently, the purpose of this current study was to determine the effect of weight bearing on hand-opening in children with cerebral palsy.*

### Notes

In an Introduction section, what conceptual component(s) occur after the Research Problem pertinent background? In the Example, the Research Problem (i.e., the reason for undertaking the research) is omitted. Such omission is not uncommon for this important component. Authors often do so thinking that the background is sufficient, probably adding the conceptual component in their own minds but not in their writing. Also absent is the Hypothesis Justification and the Hypothesis.

### Part 2 – Hypothesis justification omission

#### *Example: Introduction section*

*The anterior pituitary gland consists of six cell types, each producing a unique hormone. However, the mechanism of cellular differentiation for anterior gland cells remains unclear. Consequently, it was hypothesised that transcription factors affect the fate of a cell. To test this*

*hypothesis, the function of each of these factors was determined by adding and removing transcription factors in separate trials.*

In this example, the research problem pertinent background, research problem, hypothesis, objective, and experimental approach are stated, but the hypothesis justification is omitted.

### Revision

*The anterior pituitary gland consists of six cell types, each producing a unique hormone. However, the mechanism of cellular differentiation for anterior gland cells remains unclear. The recent indirectly supported involvement of transcription factors indicates their function in differentiation (reference). Consequently, it was hypothesised that transcription factors affect the fate of a cell. To test this hypothesis, the function of each of these factors was determined by adding and removing transcription factors in separate trials.*

### Notes

In the Revision, the addition of the hypothesis justification conveys systematic thinking by the author, fulfilling a reader's expectations. The anticipated conceptual components in each of the standard sections of the journal article are summarised in Table 1.

A third example (not shown) lacks all of the argumentative components (i.e., research problem, hypothesis justification, hypothesis). Such an argument-free Introduction is probably a consequence of extensive background information (not a focused Research Problem Pertinent Background), whereby the author mistakenly feels justified to transition from such background to the Research Objective. However, on close examination, such a background often lacks the argumentative components that justified undertaking the research.

### Summary

Of all the conceptual components in a journal article, those in the Introduction section are more

likely to be omitted because an extensive background obscures the omission. The conceptual components particularly susceptible are those constituting the argument underlying the impetus for the research: Research problem pertinent background, research problem, hypothesis justification, hypothesis. In contrast, the objective and experimental approach are rarely absent.

Taking a systematic approach to writing the Introduction section of a journal article is a useful way to avoid omitting conceptual information, which is probably obvious to the author but not the reader.

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**Table 1. Sections of a journal article: Anticipated conceptual components**

Introduction	Materials and Methods	Results	Discussion
Research problem pertinent background <sup>1</sup>	Method 1 (embedded materials)	Data Set 1 Results orientation (accomplished as a subheading)	Hypothesis support (experimental results + literature)
Research problem <sup>2</sup>	Method 2 (embedded materials)	Data verbalisations <sup>5</sup>	Limitation + counterargument + recommendation for resolving the limitations
Hypothesis justification <sup>3</sup>		Data reliability	Conclusion <sup>8</sup> + consequence
Hypothesis <sup>4</sup>		Data interrelation <sup>6</sup> (observation, trend, comparison)	
Objective		Data preliminary interpretation <sup>7</sup>	
Experimental approach		Data Set 2 (same as above)	

1. Research problem pertinent background – Information for understanding the problem. What is known as a prologue to what is not known; what is known could be preceded by the subordinating conjunction *although*.
2. Research problem – Nature of the problem: Gap in knowledge. Insufficient clarity of existing knowledge.
3. Hypothesis justification – Why the hypothesis was plausible. The most argumentative component of the Introduction. A before-the-fact perspective that justifies the hypothesis, consisting of published results, theoretical argument, and possibly a preliminary experiment.
4. Hypothesis – The cause of, or an approach for, resolving the research problem. The salient component of the scientific method. A hypothesis is general compared to an objective (e.g., the *objective of this study was to test the effect of specific hormones on inhibition of orthodontically induced tooth movement, thereby, testing the hypothesis that hormone inhibition is involved in the orthodontic process.*)
5. Data Verbalisation – A transliteration of the data (e.g., values) into a different structural form, that is, foreign language into English text (the verbalisation).
6. Data Interrelation – An observation, trend, comparison based on the data, representing the results.
7. Data preliminary interpretation – A level beyond data interrelation but short of an inference.
8. Conclusion – Pertinent to the hypothesis, not an equivalent of *in summary*.

# Medical Communications

SECTION EDITOR



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## Editorial

Dear all,

The legal side of our job is something that most of us usually give little thought to. We assume that as scientists, we are automatically on the “right side” and therefore pretty bullet-proof. Why should the law affect us, as long as we have the data to back us up? However, the reality is that this is a huge and complicated issue that can land not only medical writers, but their clients or companies in very deep hot water, very quickly.

Considering the high stakes in the

pharmaceutical industry and the highly competitive environment, it shouldn't be a surprise that rival company lawyers monitor all information coming from competitor companies, but the extent of liability that we have as medical writers might surprise and possibly scare you.

In this issue, we hear from Joanne Flitcroft. Joanne is a lawyer who has worked in the pharmaceutical industry for 17 years. She specialises in navigating the very tricky waters of defending product safety issues and maintaining corporate reputations. In her

article, she explains some common pitfalls and why we should all be paying very close attention to the legal side of our work and its implications. With Joanne's guidance, we will hopefully stay on the “right side” of the law and protect both ourselves and our clients/companies.

I'm sure you will enjoy her article, and it only leaves me to wish you the best wishes for the season – a happy and healthy 2018, and I hope Santa is kind to you all.

Bestest,  
Lisa

## Introduction to the legal implications of medical writing

Many high-profile individuals and companies have suffered harm to their reputation as a result of the content and use of emails and social media. While they may recover from such damage, reputational damage in the life sciences industry may affect the success of a company and its ability to attract investors.

However, it is not solely the use of email and social media which poses a risk. All clinical, regulatory and patient safety documentation, if inappropriately written, without regard to legal implications, has the potential to have an impact on patients, corporate reputation and affect the ability of the organisation to work effectively and efficiently.

Failure to identify and mitigate risks associated with pharmacovigilance and regulatory writing may force a company to divert resources away from drug development and into defending patient safety or clinical issues – as well as time lost handling protracted discussions with regulatory authorities.

My aim is to help you to get it right first time and to produce more effective communications and documentation. As medical writers, you work in a highly regulated environment where the documents and communications you produce may become public. The life sciences industry is subject to close scrutiny from regulatory and governmental authorities, competitors, patients, media and lawyers acting for potential plaintiffs. My aim is to provide you



with some additional tools to help you become a better writer and more effective communicator.

### The risks

The two principal legal risks arising from

inappropriately written documentation are:

- damage to corporate reputation related to the handling of pharmacovigilance and regulatory issues
- product liability claims and litigation

If a product pharmacovigilance issue is subject to litigation or an investigation, it is likely that any related documentation will be thoroughly investigated and could become public. Relevant government authorities or potential plaintiffs and their lawyers may be granted permission to obtain any documentation or communications that are relevant to the particular investigation. The impact of investigations or litigation on life sciences companies is significant. There are potentially large awards of damages, costly settlements, litigation expenses and it may impact on the financial security and viability of the company. In addition, money spent on investigations and litigation is diverted from the core business activity of the company. This may result in negative publicity and damage to reputation as well as to the product brand.

An investigation will necessarily focus on documentation dealing with sensitive information such as knowledge, data, opinions, hypotheses, analyses, ideas, which may implicate an organisation's legal position or its reputation or both, if disclosed to third parties. Pharmacovigilance and regulatory documentation is by its nature sensitive information.

## Mitigation of risks

The effective communication and management of sensitive information is a skill which is essential for all medical writers. It is important to recognise that clarity and method are critical, coupled with the appropriate classification of documents e.g. whether they are confidential or subject to legal privilege, equally important is the need to avoid concealing or censoring sensitive pharmacovigilance information or limiting the amount of information which is communicated. Sometimes documents written by medical writers may need to be disclosed to third parties through a process of discovery. Discovery is the legal process concerned with obtaining evidence by searching of documentation or conducting interviews with the authors of the documentation. The rules relating to the disclosure of documents for evidence in legal proceedings are wide-ranging and liberal and vary according to the legal jurisdiction. In addition, discoverable documentation is not limited to, for example, pharmacovigilance or regulatory documents, but may also include e-mails, calendars and even SMS messages which pertain to the medical issues discussed in such documentation.

Before you begin any medical communication, consider what it is that you are intending to achieve. Sharing medical and scientific information is not the same as communicating the information; what an author

says is not necessarily what others actually hear. Therefore, always consider the following four questions:

- What is it that you want to say?
- How do you want to say it?
- What does your audience need to know?
- What exactly do you want the audience to do with the information?

Having addressed these questions, you must then reflect on the different needs, including potential cultural differences, and perceptions of your audience and consider how the document may be viewed from an internal corporate perspective and external regulatory or public perspective.

## Practical guidance

The following is a set of guidance principles designed to assist you in your writing and to promote clarity and avoid confusion and misinterpretation:

### 1. Method of communication

Consider whether the method of communication you have chosen is the right way to document the issue. You should write documents concerning sensitive subjects with the expectation that they may be disclosed in the public sphere at some point in the future.

### 2. Facts and opinions

State facts and not opinions unless you are specifically asked to do so; you are qualified to make them and it is the purpose of the document. Avoid commenting on issues that are outside your area of expertise. If you are required to document opinions or conclusions, identify the source of the opinion or conclusion or information received. This is because it would be easy for a third party to argue at a future date that they are your opinions and that the information has been verified by the author.

### 3. Accurate and concise

Be accurate, clear and concise in your writing. Inadvertent errors of fact may be interpreted as incompetence. Do not speculate or embellish with adjectives or adverbs which can lead to misinterpretation of the information you want to communicate. By nature, they are susceptible to more than one interpretation and can easily create ambiguity. Similarly, avoid sarcasm, irony and exaggeration and gratuitous or flippant language. The recipients of your documentation or communication may forward the information to other recipients without you knowing. Your audience may misunderstand the communication and draw the wrong conclusion. Furthermore, beware of using abbreviations and

technical vocabulary. When writing your documents, assume your reader may have less specialised knowledge than you and may have a more limited understanding of the terminology. This will prevent ambiguity and promote clarity.

## 4. Neutral tone

Retain a neutral tone in your writing and avoid expressing strong feelings which have the potential to overwhelm clear thinking. Emotionally-charged expressions may also carry with them unintended weight or meaning and may be subject to misinterpretation. Similarly, avoid making defensive or critical comments.

## 5. Recording of information

Only record information which is necessary to perform your role. Don't record information which is unnecessary or considered "nice to have". Make sure you understand how to store information appropriately to ensure compliance with document retention requirements.

## 6. Documents based on limited information

Many documents which you write will take the form of more than one iteration before being finalised. If a document relating to a sensitive subject is incomplete, then indicate that the document is in draft form and is subject to change. If there is more than one draft, use numbers to denote the order in which they have been written. If you are required to write a document based on limited information it is perfectly acceptable to do so. However, it is best practice to indicate clearly that the document is based on incomplete information and that further work is needed.

## Conclusion

Poorly drafted documents can be open to misinterpretation. It is important to remember that the language you use when creating any kind of document can create the wrong impression if it is taken out of context. Choose your language carefully and always ask yourself "How would I feel if this document became public?". I hope these points have illustrated the critical nature of your medical writing and the implications from a legal perspective. The importance of being careful about everything you write about a sensitive subject cannot be overstated and I hope the practical tips help you approach your writing with confidence.

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

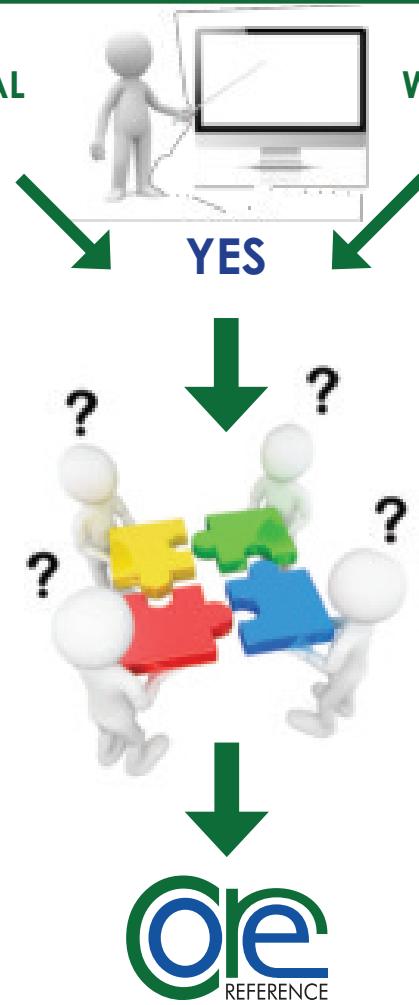
An Open Access Resource to Support Authoring of Clinical Study Reports for Interventional Studies

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

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



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



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

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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.

## SECTION EDITORS



Satyen Shenoy

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# Out on Our Own

## Editorial

Greetings, readers.

In this issue of *OOOO*, we start off with an important question – how do I prevent the risk of working too much? An apt question as we approach the end of the year, finishing up our projects and settling in to enjoy the holiday season. This is the question Belinda Cabral, our Berlin-based EMWA colleague, asked herself after she started her freelance consultancy and found herself working all kinds of hours. Many of us, especially in our early days in freelancing, have perhaps gone through such a period where

every client was welcome and we were loath to say no to a project. While such a situation is exciting and challenging in the beginning, it can eventually spiral into a stressful situation due to the pressure of multiple deadlines and a heavy workload. In her article, Belinda shares with us certain techniques that she practices in order to strike a healthy work-life balance that allows her to enjoy her downtime just as much she enjoys her freelance business.

2017 has indeed been an eventful year for EMWA's Freelance Business Group, and quite a few initiatives have been rolled out to enhance

the benefits we offer to our freelance members. And I have taken the opportunity to share these with you in a brief recap.

Many thanks to all of you who have contributed to *OOOO*; your articles are indeed insightful and of immense help to your fellow freelancers. I would also like to reiterate my request to all our readers to continue submitting your articles and sharing your thoughts with us.

Season's greetings and good luck for 2018!

Satyen Shenoy

## On my own to manage my work-life balance: How do I prevent the risk of working too much?

Regarding work-life balance, working on one's own has its advantages. For me, one of the most valuable advantages is being free to decide when I want to start and when I want to stop working. I can start working at 8am or 10am and finish at 4pm or 8pm; I can arrange my timetable to have my Friday afternoons free; and I don't have to ask for days off because of doctor appointments. In a nutshell, I am the boss of my timetable and I enjoy the flexibility. But is it really an advantage? I must say that sometimes I wish to go back to the time I was employed in a company, where I had defined worktime that I had to respect. At least, I always had my weekends and holidays free.

When I became a full-time freelancer, I kept working like the time when I was working with a company. But I noticed very quickly that it is easier to be distracted when one is not working in an office set-up. Also, it is easier to exaggerate and work late or during the weekends. So I had to think of some strategies to avoid this and find the right balance between my work and my free time.

### I choose my work time and I stick to it.

As a freelancer, there was a time when I was always tempted to check my emails, whatever the time of the day, at weekends, and during my vacations. If this was an innocent act, like: I look

As an independent worker, it happens sometimes that the clients I work for forget that I am at the service of other clients too.

very quickly and I forget about it, it would have been great. Unfortunately, when I check my emails, I also want to answer them or to do what I am requested to do, or I want to plan what I should do for work. If I do all these, then I am working. And any time this happens, it is often equivalent to working, which according to me, is not a healthy way to spend my downtime.

When I started to work as a freelancer, I did not pay attention to this and I worked most of the time. After several months, I felt tired and even got ill. I realised that as a freelancer, the times I was not in good health, my work suffered as it accumulated and there was no one to support me. So I have learned to plan my work effectively, and I have meaningful time intervals to rest and rejuvenate myself. I defined my work time and my work days, and I planned time for real vacations, during which I wouldn't work at all. Then, I inserted all of these in Excel sheets that I printed and hung on a wall in my office. Since then, I try to stick to them, even if it's not always possible (I try to stay flexible in case of deadlines or urgent work). At least, I have much more time to rest and to enjoy!

Also, I check emails and take professional calls only during my work time. When I am on vacation, I set up an out-of-office automatic reply, which allows me to fully enjoy my vacation while keeping my clients informed of my absence with

a promise to get back to them when I resume working.

### I define priorities and I say no in a diplomatic way.

As an independent worker, it happens sometimes that the clients I work for forget that I am at the service of other clients too. Some of them expect their emails to receive replies right away or their calls to be returned within an hour for regular tasks. At the beginning, I put myself under a lot of pressure and always tried to answer all emails and return all phone calls as soon as possible, until I noticed that it was not possible to do so especially when the workload grew. So I had to find a way to be there for my clients while making them understand that I can't always be immediately available to respond to their requests. Of course, some of them need to be reminded of this more often than others, but I try to do it diplomatically, and they usually understand.

But how do I prioritise my work?

First of all, I order my tasks by deadlines (which define the urgency) and then by the day I was asked to do them. Also, I deal first with tasks that are important for me.

When all my tasks are put in order of urgency and importance, I just "book" time spots on my Outlook calendar in order to perform them within my work time. That way, I know in advance if I can meet all deadlines or if I have to ask for more time to perform some tasks (instead

of working late or during the weekends). Moreover, it allows me to explain to my clients why I am not able to complete a task right away and to give them a reasonable time frame for task completion (instead of saying clearly no).

### I choose a place for my office and I only work there.

In order to really enjoy my free time, I need to forget about my work. Otherwise, I keep thinking about my work during my free time which I don't want to do. As I work on my laptop, I have the freedom to choose the location: in my office, in the living room, in the bedroom, in a café, or at the park. Unfortunately, by doing this, all these places little by little become associated with work. So when I am there during my free time, I also think of the work.

The idea I had to avoid this was to get used to working only in the same place (in my office), so that I think of working only when I am in that confinement and leave the rest of the places to be associated purely with my free time. This brought me two advantages: I am more efficient when I work and I can enjoy better my free time without



having a cloud full of work thoughts hanging over my head whenever I am out of my office.

### I lock my office door outside the defined work time.

I just imagine that when I go to my office in the morning, it is equivalent to going to work, except that I don't have to leave my apartment. As a room in my apartment serves as my office, every time I walk by it and the door is open, I see my

desk and my work stuff. So I think of the work I have to do. Since I decided to lock my office at the end of the work day, it seems like it doesn't exist at home outside my work time. In my mind, the door of my office is like a wall, so that it gives me the feeling that what is behind there is not part of my apartment (where I should enjoy my free time). I have even kept the door as simple as possible so that there is nothing particular on it that makes me think that this door belongs to my office. It is white, without pictures or signs, so that it blends well with the walls and it can be easily forgotten outside of the work time.

Of course, this works uniquely for me and I cannot assure you that it will work for others. Each person can find a way that is adapted to their life style and personality. At the end, what counts is to find the right work-life balance adapted to one's particular situation.

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# Save the date

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

For more information: [http://www.emwa.org/EMWA/Conferences/Future\\_Conferences/EMWA\\_Conferences/EMWA\\_Future\\_Conferences.aspx](http://www.emwa.org/EMWA/Conferences/Future_Conferences/EMWA_Conferences/EMWA_Future_Conferences.aspx)

## 2017 in a nutshell for the Freelance Business Group

It has indeed been a busy year for EMWA's Freelance Business Group (FBG).

We started with yet another collaboration, this time with the Verband der Gründer und Selbständiger Deutschland e.V. (VGSD; [www.vgsd.de](http://www.vgsd.de)), one of Germany's largest freelance advocacy groups. We have had a similar association with the Association of Independent Professionals and Self-Employed (IPSE; [www.ipse.co.uk/](http://www.ipse.co.uk/)) in the UK for a number of years. The main intention behind fostering such alliances is to offer the benefits of membership of such organisations to our freelancers at a discounted rate. Of course, these benefits are mostly relevant to freelancers based in the UK (for IPSE) or Germany (for VGSD). Such association memberships were a part of the Freelance Benefits Package until the latter was made redundant earlier this year. What does this mean? It means that now any interested EMWA member, whether a freelancer or not, can take advantage of these association memberships at discounted rates. This could especially be useful to those EMWA members who are considering a switch from being an employee to freelancing. Details on these membership offers and links to the organisations are provided on EMWA's website. Of course, the FBG is always interested in partnering with such organisations in other countries and request you to get in touch with us if you have a recommendation to make.

Yet another initiative implemented this year was changing the way the FBG will be managed hereon. Historically, the activities of the FBG were run by one or two or at times even three freelance advocates. However, with an increase in the scope of and programmes conducted on behalf of the FBG, EMWA's Executive Committee (EC) decided to constitute a subcommittee comprising five volunteers to look after the FBG. A call for volunteers was sent out in April this year and it was indeed encouraging to receive such a tremendous response. Subsequently, the newly formed FBG subcommittee was introduced at the spring conference in Birmingham. The FBG subcommittee members are Allison Kirsop (UK), Petra Pachovska (Czech Republic),

Paul Wafula (Germany), George Xinarianos (UK), and me (Germany). Your new FBG subcommittee has a healthy mix of experienced and relatively new freelancers, with a varied background and experience but proactive as a team and we look forward to serving the FBG to the best of our abilities. I would like to take this opportunity to thank all of you who wrote to me expressing an interest in volunteering for the subcommittee. We shall certainly be in touch should we need your help.

As the FBG continues to look after activities such as organising the Freelance Business Forum at EMWA conferences and putting together the Out on Our Own section of *Medical Writing*, I would like to share a couple of new initiatives that are in the cards.

The Freelance Directory (FD) provided on EMWA's website is a useful tool for our freelancers to advertise their business. This is by no means a novel concept. EMWA's American and Australasian counterparts have similar facilities for their members. While FD has a positive feedback overall, some of you informed us that it was somewhat tedious and clunky and needed to be revamped. Taking these suggestions into consideration, the FBG subcommittee (especially Allison and Petra), together with Alison Rapley, our former president, are involved in redoing the FD to make it more dynamic, upfront, and "search-friendly". Our goal is to create a FD that provides improved visibility and a much easier

interface between our members who subscribe to the FD and their potential clients.

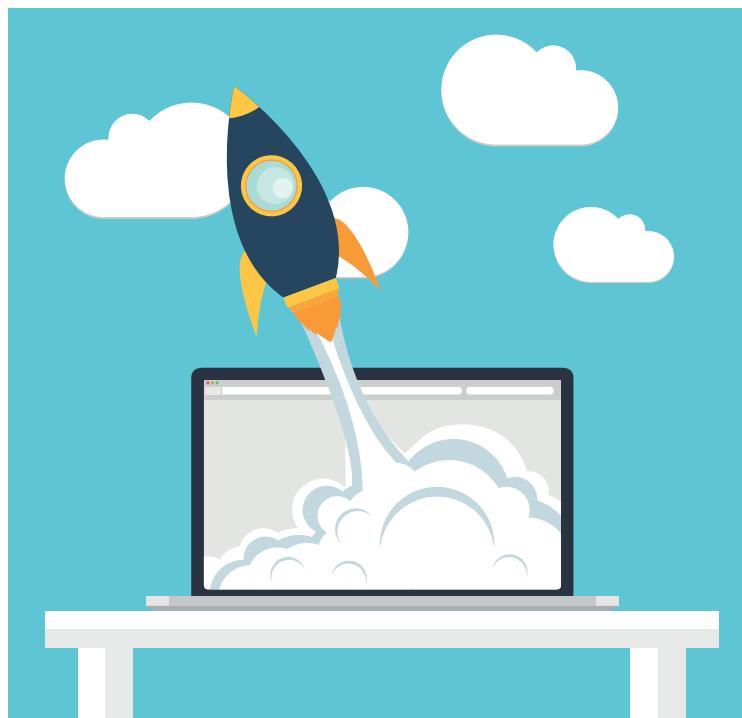
The FBG conducts the Freelance Business Survey (FBS) every 3 years to gauge the practices among our freelancers, and the next survey will be conducted in early 2018. Over the years, the FBS has taken a more holistic approach and now collects responses to a number of diverse issues that are relevant to the freelancing business. The results of the FBS are of significant importance to not only the FBG and EMWA's EC but also to current and future freelancers. For example, if a newbie freelancer wonders what the current hourly rates are for drafting a manuscript, one of the easier ways they can get this information is by looking at the survey results and... et voilà! Of course, to achieve a real-life representation, we need participation from as many members as possible. To consider the example I just gave, if the results on hourly rates were based on the output of a few freelancers whose rates are either at the high end or at the low end, the rate we arrive at is unrepresentative of current practices. And this can potentially affect our business.

My intention behind sharing the progress made by the FBG in 2017 is straightforward: I want to present a snapshot of all the activities we carried out for the benefit of our freelancers in 2017. And we have you to thank for it because these ideas, sometimes even in a rudimentary form, have come from you, during a casual conversation while at the EMWA conferences,

during an informal local gathering of freelance medical writers, via email messages, or on social media. It is your participation in the process that allowed us to take on these initiatives and implement them. Which is exactly why I have also taken the opportunity to apprise you of what is coming in the near future, and to request that you continue to participate in our initiatives and make them successful. If perchance you have other ideas that you think would be beneficial to our freelance membership then please share them with us.

I wish you all a successful 2018.

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# Upcoming issues of **Medical Writing**



**March 2018:**

## Vaccines and immunotherapies

This issue will be about regulations, study design, outcomes, analysis, and other issues specific to vaccines and immunotherapies.

**The deadline for feature articles is December 11, 2017.**



**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.**

### 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/>