

Volume 26 Number 3
September 2017

Medical Writing



Observational Studies

Also in this issue...

- Patient-reported outcomes: How useful are they?
- EMA releases the revised GVP Module V – updated guidance on risk management plans
- Mentoring tomorrow's medical writers



EMWA 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

Observations and Observational Studies

Our publication, *Medical Writing*, has always been a work in progress, continually evolving to meet our members' needs and desires. Originally a four-page newsletter called the *EMWA Newsletter*, it was renamed *The Write Stuff* in 1998 and, under the guidance of Elise Langdon-Neuner, grew to a larger publication renamed *Medical Writing* in 2011. Since taking over as Editor in 2012, I have focused on shifting *Medical Writing* to an in-house publication and to a more dynamic format.

Due to the recent addition of a Managing Editor, Victoria White, I have finally had a moment to take a step back and reflect on how far we have come. Thanks to Chris Monk, our layout specialist, as well as Vicki, the Editorial Board, and contributors, we are producing a visually impressive publication full of high-quality, practical articles. And based on the comments I have received, it is considered a key and valuable benefit of EMWA membership. I also know that it's a great calling card for our association and members. I am happy with what we have accomplished, and I want to sincerely thank everyone who has contributed.

This issue of *Medical Writing*, which focuses on observational studies, is a great example of the high quality of our journal – it's packed full of great articles on observational studies, as well as all kinds of other useful information. The issue begins with an article by **Maria Kołtowska-Hägström** on the basics of observational studies. She explains what

observational studies then are, how they differ from randomised clinical trials, why their importance in evidence-based medicine is increasing, and how patient registries



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and research databases can be used as a source of medical information. **Tom Lang** follows with an article on the basic terminology and statistics used in observational studies to describe risk and association. **Willi Sauerbrei and colleagues** then talk about the STRATOS initiative, which aims to provide guidance for the design and reporting of observational studies, and **Andrea Rossi and colleagues** describe the guidelines available for reporting observational studies in peer-reviewed publications. Meanwhile, **Namrata Singh** and **Vasudha** update us on the current status and expected changes in requirements for registering and obtaining ethics committee approval for observational studies. Articles by **James Visanji** and **Greg Morley** cover the regulatory aspects of NI-PASS (non-interventional post-authorisation studies), which are used to collect data on approved products and **Karin Eichele's**, in her section "The Webscout," summarises information available on the web about observational studies.

Looking at the last few issues, I am honestly blown away.

Also in this issue

This issue of *Medical Writing* also includes excellent articles on subjects unrelated to observational studies. **Silvia Paz Ruiz** discusses the usefulness of patient-reported outcomes, and **Tiziana von Buchhausen and Sven Schirp** present the EMA's Good Pharmacovigilance Practice Module V, which provides updated guidance on risk management plans. Finally, **Kathryn Lee** talks about the importance of mentoring tomorrow's medical writers and how you can help.

President's Message



Dear EMWA Members,

It's autumn again and most of you will have returned from your vacations by now re-energised and ready for the year ahead. The Executive Committee has been busy planning our conference in Cascais scheduled for November 2-4. We are planning to hold 29

Foundation and Advanced level workshops, along with the Introduction to Medical Writing session, early morning yoga, and some interesting social events. Cascais will certainly provide a lovely learning environment with plenty of opportunities for networking and discussions.

You might have already noticed that our website has a new look and we have now significantly improved its response time. The website platform has enabled us to create an easily searchable freelance directory and archive of past EMWA webinars. This is a definite improvement and we would appreciate your having a look. Your feedback will be greatly appreciated by our Web Manager Diarmuid De Faoite.

In order to continually strive to provide our members with well vetted and relevant information, we will soon start sending out short EMWA News Blasts via email announcing important information on conferences, webinars, and general information of interest to our members. These will be sent out at the beginning of each month. If you have any newsworthy

items, please contact our Public Relations Officer Maria João Almeida.

Forthcoming webinars include an "Introduction to Clinical Evaluation Reports for Medical Devices", and "The Cardiovascular System." Please check the EMWA website for the dates and times of these new webinars.

We are also busy lining up topics and speakers for the next series of Expert Seminar Sessions and for the Symposium on Medical Devices scheduled for the annual meeting in Barcelona on May 1-5, 2018. Mark this date in your calendar as this is sure to be an exciting conference.

I hope you enjoy reading this issue of *Medical Writing* dedicated to Observational Studies put together by our very capable Editor-in-Chief, Phil Leventhal.

I look forward to seeing you all in Cascais. Adeus!

Abe Shevack

asp scientist@googlemail.com

A scenic photograph of a rocky coastline with blue water. The rocks are dark and jagged, and the water is a vibrant blue. The text "Save the date" is written in large, white, bold letters across the top. Below it, "Cascais, Portugal 2017" is written in a similar font. The text "The 45th EMWA Conference in Cascais, Portugal will be held on 2-4 November 2017 at the Cascais Miragem Hotel." is written in a smaller, orange font. At the bottom, the URL "http://www.emwa.org/EMWA/Conferences/Future_Conferences/EMWA/Conferences/EMWA_Future_Conferences.aspx" is written in a small, white font.

Save the date

Cascais, Portugal 2017

The 45th EMWA Conference in Cascais, Portugal will be held on 2-4 November 2017 at the Cascais Miragem Hotel.

http://www.emwa.org/EMWA/Conferences/Future_Conferences/EMWA/Conferences/EMWA_Future_Conferences.aspx

EMWA News

Editorial

In this issue, we are bringing to you many updates on different aspects relevant to our medical writing community. Tim Koder from Oxford PharmaGenesis introduces the Open Pharma project, which aims to promote and aid a faster and more transparent publication of medical research. Lillian Sandø, one of the few EMWA members with an ELS suffix, shares her experience with the BELS exam organised for the first time since 1966 in collaboration with the EMWA conference in Birmingham. I personally adhere to her words,

and would like to encourage both our editors and writers to take this exam in the future. Also, since our website has been switched to an improved platform, Diarmuid De Faoite tells us all the improvements that this update entails. We urge you to visit the new website if you haven't done it so far. Finally, Amy Whereat shares the news from the medical writers' get-together this summer in Paris. If you're a medical writer living in France, you can learn what is going on and we welcome you to join the group as well as the upcoming meetings.

SECTION EDITOR



Evguenia Alechine

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Last but not least, we would like to remind you that there is the possibility to volunteer for EMWA's various committees and groups, and we remind you to check and register for the many activities available at the forthcoming conference in Cascais, Portugal.

Evguenia

Driving innovations in medical publishing: The Open Pharma project

Open Pharma is a new initiative to drive rapid and transparent publication of medical research. A group of pharmaceutical industry leaders, academics, publishers and other stakeholders is exploring innovations in academic publishing to improve the dissemination of pharmaceutical research.

In the words of Dr Richard Smith, former editor of the *BMJ* and chair of Open Pharma, the current publication model is "slow, inefficient, corrupt, wasteful and expensive". This has a negative impact on biomedical research and, ultimately, patient healthcare. While pharmaceutical companies fund more than half of all biomedical research, to date they have had little involvement in advancing the model of scientific publishing. The vision of Open Pharma involves helping pharmaceutical companies to use their position as major research funders to drive innovation in medical publishing and create a new model that is fast and transparent. The group is currently concentrating on four areas of innovation: open access; ORCID, CRediT, and Convey; preprints and post-publication peer review; and layered publication models.

To learn more and give your views, visit the Open Pharma blog at <https://openpharma.blog>.

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Call for volunteers

As you all know, EMWA is run by our members and relies on them to develop and support all our initiatives. There are currently a number of vacancies for EMWA members to get involved with various groups. This is a great opportunity to develop your skills and experience at the same time as helping to promote the role of medical writers and strengthen our association. If you are interested in getting involved or want more information please contact info@emwa.org.



Certified syntax snob: My BELS Exam experience in Birmingham

“What’s wrong with sentence 1? A: punctuation error, B: wrong word use, C: error of logic, D: dangling modifier”. That’ll be D, thanks – dangling modifier. One of my pet peeves. A freebie among the 100 or so questions of the BELS certification exam, which I took on a sunny May afternoon in Birmingham – my warm-up for the EMWA spring conference. I was thrilled to learn that the conference coincided with the 2017 European BELS exam. Earning the certification has been on my wish list for a few years, and finally the time and place presented themselves. As a medical writer in a pharmaceutical company, I don’t strictly *need* the certification, but it

sure feels nice to have. A nice proof of editorial proficiency in a profession where most of us don’t have a degree in linguistics or communications, yet depend on those skills. Was it hard? Yes and no. It was a great mix of very easy to very hard questions, covering most types of problems an editor in the life sciences comes across. For a syntax geek and grammar snob, it was also quite fun. Being tested on some of your pet peeves – what’s not to like?



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The new EMWA website is live! Faster, more legible, and mobile responsive!

The EMWA website (www.emwa.org) has switched over to a new platform. Although the new website looks very similar to the old one, there is a marked difference in its speed and responsiveness.

We have also taken this opportunity to modify some of the styling. The font used is now optimised to make the online text more readable. The new template is also fully mobile-responsive, so all sizes of screen from the smallest smartphone screen up to a full 4k display, will display the website properly.

Other technical modifications have also been made to the website that will not be visible to the general user – e.g. improved encryption.

Our sincere thanks go to the Kingston-Smith team at EMWA Head Office who worked very hard to deliver the newly revamped EMWA website.

Please let us know if you have any issues with the new website, or any general comments regarding it. Equally, please also feel free to reach out if you would like to contribute content to the EMWA website.

Diarmuid De Faoite
EMWA Website Manager
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Medical writers getting (it) together in Paris

Photo: Bigstock

With summertime upon us, the medical writers and communicators in France got (it) together again in Paris on the 12th of June 2017. This growing network of medical writers, translators, and communicators spent a very sociable evening networking before getting down to some “serious” business. As this was now our fourth meeting since last year, it was time to set some objectives to keep the group alive and kicking. This is what we discussed.

EMWA Birmingham

Those who had attended the EMWA conference in Birmingham gave a short overview of their impressions from the conference. Trevor Stanbury (Unicancer) reminded the group that disclosure requirements concerning layman summaries, clinical study reports, etc. are becoming increasingly complex and thus will require more medical writing support. Also, data sharing will come into effect July 2018. We do not know how many researchers in France are aware of these requirements today and whether they have the resources to produce these documents in English. We discussed whether this could be an opportunity for medical writers to provide this support. However, we all agreed that there were likely to be budget issues, considering the current lack of funding for medical writing in some sectors.

The role of the medical writer

The lack of recognition for medical writers in France became apparent as the group discussed the various issues each of us face. First, there is a general lack of awareness of medical writing as a career in France. This became obvious as the

freelance medical writers shared the different professional codes they were assigned at the creation of their activity. They ranged from artist to training journalist. Apart from being a quirky fun fact, this does pose a problem for some writers who are unable to obtain funding to attend the EMWA conference, as EMWA is not a recognised training organisation for certain professional codes. Also, some writers expressed having inappropriate indemnity insurance, as insurers struggle to classify their *relative risk!* Amy Whereat informed the group that EMWA has negotiated an appropriate insurance plan for medical writers and a discount is available for EMWA members. Details can be found on the EMWA website (<http://www.emwa.org>).

Several members of the group identified the lack of job announcements for medical writers and recounted landing their jobs completely by chance. Others spoke of their continual need to explain their role to their internal customers. Michelle Newman highlighted that basic scientists are also unaware of medical writing as a career choice and suggested promoting the role of the medical writer to PhD students and post docs at local career days. This is planned for “La rentrée” (September/October). Amy Whereat added that this was also an EMWA objective and that EMWA would support us using the presentation material available on the EMWA website.

Some research groups currently face various funding problems for medical writing support for publications. Many posts in the clinical trial process are recognised but writing the manuscript is still considered the responsibility of the researcher. Some medical writing posts are

therefore seen as an additional cost. This problem will be complicated to address quickly. The group decided to work on raising the profile of the medical writer as a first step. Results of the Diazepam Study (*Difficultés des Auteurs à la Publication d'Articles Médicaux*) conducted by Martin Duracinsky (AP-HP), Olivier Chassany (AP-HP), and Fabienne Péretz (Abelia Science) outlines the difficulties French researchers face when publishing has recently been published in the *BMC Medical Research* journal.¹ Others have contacts with which we can speak.

The freelancers in the group suggested that we create a jobs board for agency and overflow jobs. Plan of action:

1. Find a better name for the group.
2. Create a website to create awareness about the group and medical writing in general.
3. Share jobs post members via the LinkedIn group (www.linkedin.com/groups/5173211), which will then be transferred to the website once it is up and running.

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References:

1. 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.

RCTs: Can the treatment work? Patient registries: Does the treatment work?

Patient registries and research databases as a source of medical information

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Abstract

The first part of this article compares the main features of studies based on patient registry data with those of randomised clinical trials, providing a basis for better understanding the differences between the two. The second part details how to report study-specific issues with patient registries, such as study objectives, patient populations, bias, confounders, missing data, study duration, and gives a few tips on how to improve the credibility of papers based on patient registry data.

Evidence-based medicine: patient registries and randomised clinical trials

Evidence-based medicine (EBM) strictly classifies different sources of medical information by the strength and reliability of the evidence they provide. In this EBM hierarchical model, meta-analyses and systematic reviews are on the top of the pyramid, and are closely followed by randomised clinical trials (RCTs), particularly blinded and controlled ones. Patient registries fall under observational studies and are classified as low-level evidence (Figure 1). RCTs are considered to be the golden standard of medical evidence primarily because of being a reliable



unbiased source for inferring causality from observed associations.¹ However, the reality is not always so clear and straightforward. The main concern related to RCTs as guidance in medical decision-making is their applicability to daily clinical practice and generalisability to a patient population at large.

RCTs are medical experiments with a pre-defined hypothesis – they are designed to confirm or deny the hypothesis; in other words, they should provide the clearest possible answers as to whether a given intervention works. To get such a clear and definite answer, the RCTs must be performed in a *noise-free environment*, almost as in a sterile laboratory where the only difference between the study and control arms is the intervention. Randomisation is one way to ensure this. Another is a list of subject selection criteria that are specific and often long. Both randomisation and specific inclusion and exclusion criteria ensure that the study population is homogenous and study arms similar (Figure 2). Obviously, designed in this way, RCTs are suitable for the purpose they serve i.e. to capture the efficacy of the studied intervention. However, what happens next, once the efficacy of an intervention has been proven and the new drug enters daily clinical practice? The results of RCTs are verified in patients who often do not resemble those from clinical study (Figure 3).

This problem is illustrated by Carter and colleagues, who analysed the inclusion and exclusion criteria from 17 RCTs on ulcer treatment (venous, diabetic foot, and pressure ulcers) and calculated the proportion of a typical wound-care patient population that would have been excluded from the studies. This proportion served as a surrogate for study applicability to daily clinical practice. The authors estimated that more than 50% of patients would have been ignored in 15 of 17 studies and, therefore, they concluded that these results are unlikely to effectively support management of a typical wound-care population.²

To better understand the role that a patient registry plays in medical decision-making and to capture the main differences between registries and RCTs, let's start with the definition. According to the Agency for Healthcare Research and Quality, "A patient registry is an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or

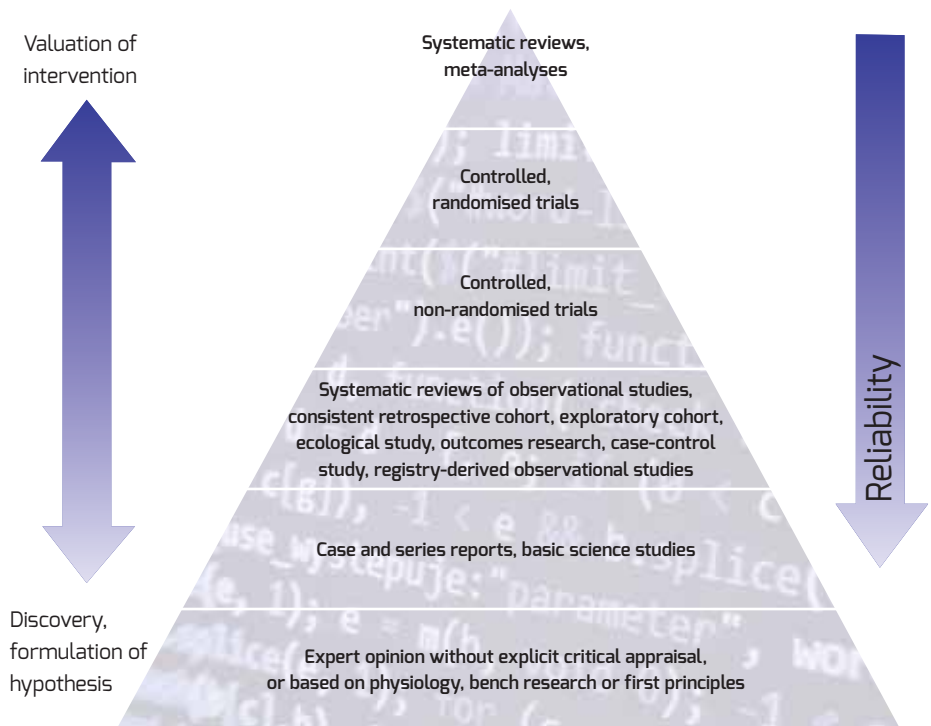


Figure 1. Pyramid of medical evidence hierarchy according to evidence-based medicine.

Based on: the UK National Health Service, US Preventive Services Task Force, <http://www.cebm.net> (accessed June 22, 2017) and Vandembroucke JP. Observational Research, Randomised Trials and two views of Medical Science; PLoS Medicine 2008

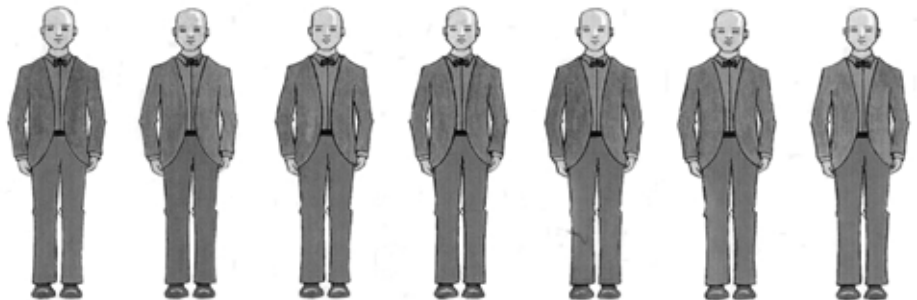


Figure 2. Homogenous randomised clinical trial patient population, courtesy of Dr Henri Wallaschofsky, Germany



Figure 3. Heterogenous and diverse daily clinical practice patient population, courtesy of Dr Henri Wallaschofsky, Germany

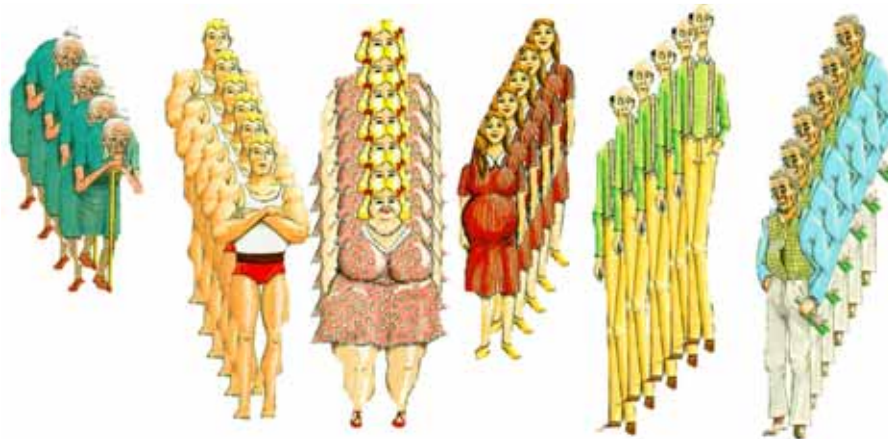


Figure 4. Patient registry multiplication of daily clinical practice patient population

exposure, and that serves one or more pre-determined scientific, clinical, or policy purposes.”³ The definition captures the most important aspects of patient registries, such as applicability of observational study methods, the need for standardised data collection, evaluation of pre-defined outcomes and identification of registry populations. Furthermore, it also underlines that the purpose of a registry should be determined beforehand, implying that data collection is purpose-driven, not the other way around, i.e. the goal of analysis is driven by the collected data. In the same user guide for patient registries, the Agency for Healthcare Research and Quality distinguishes among the following purposes of registries:³

1. to describe the natural history of diseases
2. to evaluate the effectiveness or cost-effectiveness of healthcare interventions
3. to collect information on safety
4. to focus on quality of care

Finally, each type of patient registry can be further characterised by the population enrolled, e.g. by a disease, phenotype, exposure to drug or

medical intervention, region of origin, or pre-defined features.

The principle distinction from RCTs is the fact that in registries patients are treated according to clinical practice, i.e. treatment and patient management are at the discretion of the treating physician, whereas in RCTs intervention is dictated by a protocol. Additionally, commonly, patient registries are run for a long time, collecting information on a large number of patients and cover many countries and regions whereas RCTs are of limited duration and enrol a strictly limited number of subjects, based on sample size calculations. The large number of enrolled patients replicates various types of patients managed in daily clinical practice and thus it allows for subgroup analyses (Figure 4). These properties are crucial particularly for registries focusing on rare disorders in which prevalence and incidence are per definition low, and therefore solely registries are capable of providing enough data to draw meaningful conclusions. The main differences between registries and RCTs are summarised in Table 1.

Table 1. Main differences between randomised clinical trials and patient registries

Characteristics	Randomised clinical trial	Patient registry
Patient management	According to the protocol	According to clinical practice
Selection criteria	Very stringent	Much less stringent
Duration	Fixed	Often open-ended
Comparator	Often as part of the study	Various (e.g. part of the study or general population)
Bias	Low risk	High risk
Generalisability	Low	High
Applicability to target population	Various	High

Safety is another important field where a patient registry is a valuable tool to collect rare adverse events or atypical treatment reactions, which are unlikely to be captured in RCTs due to their limited size and duration (Figure 5). Furthermore, a patient registry may provide clinical context for adverse events reported spontaneously. Patient registries are often used to fulfil health authority requirements, for example running post-marketing authorisation surveillance studies.

Finally, it should be highlighted that frequently it is impossible or unethical to perform an RCT and medical-decision making has to be based on evidence derived from observations. Smith and Pell in a humorous way presented the results of systematic review of RCTs on the use of a parachute during free fall. Obviously, they could find no RCTs so they concluded: “As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials.”⁴

As a result, many taskforces and working groups involved in Grading of Recommendations, Assessment, Development and Evaluations (GRADE) suggest that observational studies may provide stronger and more relevant evidence as long as they are of high quality and the data are reported in a balanced and comprehensive way.⁵

Publishing patient registry data: how to maintain high quality?

Overall, publishing patient registry data follows the same rules as publishing any other scientific data with clarity, conciseness, accuracy and precision being the milestones of high quality. Moreover, the completeness of published information related to the study design and methodology allows readers to properly evaluate the value and reliability of presented results.⁶

As already said, a patient registry uses observational methodology and, therefore, reports of their data should be in line with the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) guidelines. These help researchers to share their work in a transparent way, and to select enough information for critical assessment of the study design, conduct and analysis – in other words sufficient information to evaluate the credibility of their work.⁷

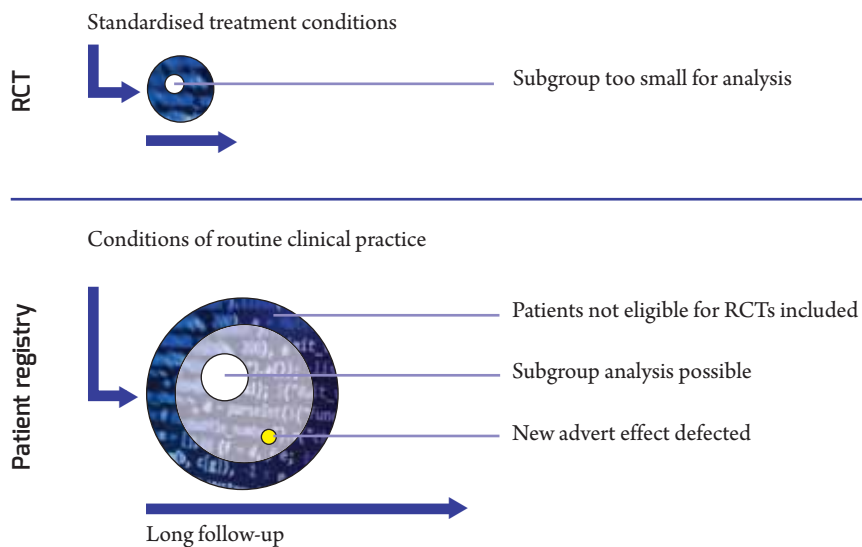


Figure 5. Safety assessment in randomised clinical trials (RCTs) and patient registries, courtesy of the late Dr Bernhard Saller

Despite the fact that these general rules and recommendations apply to publications on patient registry data, a few specific issues are worth discussing in detail.

Objectives and methods:

As for any other publication, the objectives of the study or analysis must be specified, and the methods section needs to effectively describe the way the study was performed, particularly how it addressed the objectives. At the same time, this section aims at convincing readers that the way the data were collected and analysed guarantees high quality, reliable, robust results. However, it seems that for patient registry papers this section is even more important than for papers reporting RCT results; there is no strict protocol behind a patient registry, so at least in theory there could be more room for data manipulation.

A few tips:

1. Study objectives – always separately describe the general purpose of a patient registry and the specific aims of the presented study using a subset of patient registry data. If you analyse all data, also clearly state that the purpose of the study was the same as for the general purpose of the patient registry. For example, Odeyemi et al used the data from the General Practice Research Database (GPRD) in the UK to study overactive bladder (OAB) symptoms. They first described

GPRD as a longitudinal general practice database collecting data from a representative sample of general practices in the UK, and then specified the purpose of their study: to estimate the incidence and prevalence of OAB symptoms; to analyse the use of anticholinergic/antispasmodic drugs and healthcare resources.⁸

2. Description of patient population including selection criteria – as with the objectives, the selection criteria for a registry and for the specific study should be discussed in detail. This is very important not only to understand whether the analysed population reflected that of the registry but also whether it was representative of the target patient population. It can happen that a registry population constituted a good representation of the patient population but the analysed cohort did not. On the other hand, sometimes the analytical dataset aims to include all patients in the registry, and only excludes patients with incomplete data for pre-defined variables. An example is the analysis of fracture risk in adult patients with growth hormone deficiency (AGHD), both untreated and treated with growth hormone.⁹ The authors first referred to the already published Hypopituitary Control and Complications Study (HypoCCS) and then described its specific inclusion and exclusion criteria. Secondly, they selected the following variables as inclusion criteria for their study: age, sex, disease onset (adult onset or childhood

onset), at least one follow-up visit after study entry, treatment with growth hormone. Only patients with no missing information for all of these pre-defined variables were included in the study.

3. Duration – Here it is very important to precisely report the timeframe when the data were collected, preferably in calendar dates, or at least years, and also the follow-up time. Usually, registries continuously enrol patients, so at the time of analysis (database cut-off point) patients have been followed for various durations, i.e. some of them may have been enrolled for many years before the database cut-off point, and some for just a short time, very close to the time of analysis. Therefore, it is recommended to report median and percentiles (or range) of follow-up, not the mean, which can be misleading. Using the KIMS database (the registry of AGHD), Tritos et al compared AGHD caused by different underlying aetiologies; they reported that the median follow-up was 6.7 years for one aetiology group and 5.8 years for another with a range of 0-18 years.¹⁰ No doubt, the medians provide much more precise information. Furthermore, studies with long-term follow-up should report the number of patients per year of follow-up.¹¹

4. Endpoints or outcomes – As with RCTs, it is critical to clearly define the study endpoints or outcomes to be evaluated in the analyses. These should be defined before retrieval of the patient data begins and before the analyses are performed. Sometimes, researchers decide to check the availability of the data before they decide which outcomes should be included; this is done by simple frequency tables including the number of patients with missing and non-missing data for given variables. The HypoCCS paper on fracture risk clearly defines all outcomes included in the analyses, and especially clearly the fractures: how the data were collected; how they were defined and categorised.⁹

5. Ethical aspects – Often these aspects are discussed and the need for patient informed consent and ethics committee approval is questioned. In the majority of countries both are needed, and at least obtaining ethics committee opinion should be a standard.

6. Statistical methods – Applying proper statistical methodology is absolutely crucial for the credibility of results; therefore, this section must not be neglected. In simple descriptive studies, simple descriptive statistics are enough,

but whenever researchers deal with more sophisticated questions such as comparisons between treatment groups, prediction of treatment outcomes, or mortality analysis, more advanced techniques must be used. Basically, in registries, treatments are not randomised, so patients belonging to one group may be systematically different from another group (e.g. treatment group vs. non-treated group). The analysis must consider such selection bias, and that is where advanced statistical methods come into place and must be precisely described in the paper. Similarly, the statistical analysis should account for all known or potential confounders. A paper based on the data from the KIGS registry (children with short stature treated with growth hormone) analysed changes in body mass index (BMI) during long-term growth hormone treatment. The change in BMI was compared in various primary aetiology groups; since there were differences between patient groups before growth hormone treatment started, the authors had to use advanced statistical methods, and these are well described in the paper.¹²

Results and discussion:

1. Results – General rules relating to the presentation of results also apply to papers based on a patient registry, namely that the way the results are presented needs to be factual, structured according to the study objectives, providing exact data and avoiding interpretation. The STROBE guidelines provide a very comprehensive guide for how to present results.¹³

2. Completeness of data – The level and type of missing data should be predicted at the time of study design and further assessed when data are being cleaned and analysed. Depending on the extent and type of data missing (missing completely at random, missing at random, missing not at random), different statistical approaches can be employed.³ This approach needs to be precisely described in the statistical method section. Nevertheless, good practice recommends reporting the number of observations on which given results are based. This is clearly seen in the table of baseline characteristics for the 2,589 patients with AGHD in whom cardiovascular risk factors were analysed in the KIMS study. The column *number*

Does it work? How does it work in real life?

Patient registries answer these questions.

of non-missing shows that almost complete data were available for lipids and blood pressure but information on body composition was available only in a proportion of patients.¹⁴

3. Study limitations – This section is particularly important in papers reporting patient registry data. It should cover not only aspects relating to certain analyses but also general issues inherent to this type of research. The importance of identification and discussion of study limitations (bias, confounding, imprecision) is highlighted in the STROBE guidelines. The guidelines also recommend referring discussed limitations to other studies in terms of validity, generalisability and precision.¹³ The already cited analysis on fracture risk addresses a number of limitations, and whenever possible explains the attempts to minimize their impact on the credibility of the results. As an example, the authors recognised that patients on growth hormone treatment differed from untreated patients, so the statistical analyses accounted for identified confounders; however, residual confounding could exist which is acknowledged in the discussion.⁹

4. Conclusion – The general rule is that studies performed with registry data do not prove causality and can solely indicate associations between observations. Indeed, this rule should be followed and conclusions must be drawn with caution, taking into consideration the nature of the study, potential sources of bias, confounding, including residual and unknown confounding and imprecision.¹³ The results of sensitivity analyses and subgroup analyses may help formulate balanced and reliable conclusions.¹¹

To summarise, both types of studies, RCTs and those based on patient registry data, provide useful medical information: RCTs answer the question, “Can it work?” Patient registry data – studies answer the questions, “Does it work? How does it work in real life?”

Acknowledgements

I would like to thank all patients who contribute their data to registries and who, in doing so, help us understand diseases and improve daily clinical care.

References

- Altman DG. What randomized trials and systematic reviews can offer decision makers. *Horm Res* 1999;51(suppl 1): 36–43.
- Carter MJ, Fife CE, Walker D, Thomson B. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. *Adv Skin Wound Care* 2009;22:316–24.
- Gliklich R, Dreyer N, Leavy M, editors. Registries for evaluating patient outcomes: a user’s guide. 3rd ed. Two volumes. AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. <https://effectivehealthcare.ahrq.gov/topics/registries-guide-3rd-edition/research/>.
- Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *Br Med J* 2003;327:1459–61.
- Atkins D, Best D, Briss PA et al. Grading quality of evidence and strength of recommendations. *Br Med J* 2004;328:1490.
- Gattrell WT, Hopewell S, Young K et al. Professional medical writing support and the quality of randomised controlled trial reporting: a cross-sectional study *Br Med J Open* 2016;6:e010329. doi:10.1136/bmjopen-2015-010329.
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP for the STROBE Initiative; The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.
- Odeyemi IAO, Dakin HA, O’Donnell RA, Warner J, Jacobs A, Dasgupta P. Epidemiology, prescribing patterns and resource use associated with overactive bladder in UK primary care. *Int J Clin Pract* 2006;60:949–58.
- Mo D, Fleseriu M, Qi R et al. Fracture risk in adult patients treated with growth hormone replacement therapy for growth hormone deficiency: a prospective observational cohort study. *Lancet*



- Diabetes Endocrinol 2015;3:331–8.
10. Tritos NA, Johannsson G, Korbonits M et al. Effects of long-term growth hormone replacement in adults with growth hormone deficiency following cure of acromegaly: a KIMS analysis. *J Clin Endocrinol Metab* 2014; 99(6):2018–29.
11. Koltowska-Hägström M, Mattsson AF, Monson JP et al. Does long-term GH replacement therapy in hypopituitary adults with GH deficiency normalise quality of life? *Eur J Endocrinol* 2006;155:109–19.
12. Reinehr T, Lindberg A, Koltowska-Haggstrom M, Ranke M. Is growth hormone treatment in children associated with weight gain? Longitudinal analysis of KIGS data. *Clin Endocrinol* 2014;81: 721–6.

Does it work? How does it work in real life?

Observational studies/
patient registries

13. Vandenbroucke JP, von Elm E, Altman DG et al, for the STROBE initiative. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 2007;147:W-163–W-194.
14. Abs R, Feldt-Rasmussen U, Mattsson AF et al. Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults – a KIMS database analysis. *Eur J Endocrinol* 2006;155:79–90.

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Odd cases and risky cohorts: Measures of risk and association in observational studies

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Abstract

Hundreds of statistical tests, procedures, and descriptive measures are used in clinical research. Risks, odds, and hazards are among the most common but not always the most understood. They are often used in all three types of observational studies in medicine and epidemiology – case-control, cross-sectional, and cohort studies – so a good understanding of what they are and are not is helpful in understanding these studies. Here, I briefly describe these measures, how they are used in observational studies, and how to interpret them.

Introduction

The three major types of observational studies in medicine and epidemiology – case-control, cross-sectional, and cohort studies – often involve three common measures of risk: odds, risks, and hazards and three common measures of association: odds ratios, risk ratios, and hazards ratios. Here, I briefly describe these measures, how they are used in observational studies, and how to interpret them.¹

Measures of frequency

How often or how likely an event occurs can be indicated with a “measure of frequency.”

Proportions

A **proportion** or fraction is a measure in which



the numerator is a subset of the denominator: “fetal deaths ÷ all deaths”. Proportions are often expressed as percentages: fetal deaths are a percentage of all deaths, for example.

Rates

A **rate** is a change in proportion over time, although sometimes the time period is assumed or not specified. For example, “the fetal survival rate was 90%” means that 90% of the infants alive at the beginning of a given period were alive at the end of the period.

Ratios

Finally, a **ratio** is a relationship between two independent quantities in which the numerator is *not* a subset of the denominator. For example, the fetal death ratio is expressed as “fetal deaths: live births.”

Measures of risk

Prevalence

Prevalence (and incidence) are not strictly measures of risk, but they are relevant here.

Prevalence is the proportion of people with the disease divided by the total number of people in whom the disease can occur. Thus, it is the proportion of people with the disease at a given time:

**The prevalence of prostate cancer in 2011 =
16.9 per 1,000 men, or 1.69%**

Incidence

Incidence (sometimes called **instantaneous incidence**) is the **rate** at which new cases are diagnosed; that is, the number of new cases identified in a given (usually shorter) period among all people in whom the disease can occur:

**The incidence of prostate cancer in 2012 =
105 per 100,000 men, or 0.11%**

Another common incidence rate is **cumulative incidence** (also called the **incidence proportion** or **cumulative proportion**; no sense in making things easy), which is a measure of disease frequency during a longer period of time and often for a specific subpopulation:

The cumulative incidence of prostate cancer in black men up to age 69 years is 15.0%.

Risk

Risk is the probability or the frequency of an unfavourable event occurring during a given period of time. (Risk can also refer to positive events. In such cases, “risk for benefit,” may be a more accurate term. We don’t talk about the “risk of a happy marriage,” for example). How risk is reported is important. A risk of 1 in 20 is often seen as lower than a risk of 1 in 43 when in fact it indicates a higher risk. Similarly, a risk of 1 in 20 appears to be lower than 10 in 200, although the risk is the same. Finally, a probability of 6 in 100 is the same as 6% and 0.06, but each tends to be interpreted differently.

Absolute risk, or simply **risk**, is the probability that a specified condition will affect the health of an individual or a population (in other words, the incidence):

$$\text{Risk of prostate cancer} = \frac{\text{No. men with prostate cancer}}{\text{No. men in whom prostate cancer can develop}}$$

In epidemiology, absolute risk may also require a defined geographical area and period. By convention, the estimated population on July 1 (mid-year) is used in the calculation.

$$\text{Absolute risk of prostate cancer for men living in London in 2017} = \frac{\text{No. of men in London with prostate cancer in 2017}}{\text{Estimated No. of men in London as of July 1, 2017, in whom prostate cancer could develop}}$$

The next several examples are based on a study in which 14 of 200 men with prostate cancer treated with resection died, whereas 30 of another 200 men with prostate cancer treated with watchful waiting died.

The absolute risk of death from prostate cancer with watchful waiting (no treatment) is 15% (30 ÷ 200). The absolute risk of death from prostate cancer with prostate resection is 7% (14 ÷ 200).

The **absolute risk difference, attributable risk, or absolute risk reduction (ARR)** is simply the difference between two absolute risks. Using the above example:

The absolute risk difference in mortality from prostate cancer treated with resection as opposed to watchful waiting is 8%. (From the above data, 15% – 7% = 8%). In other words, when compared to watchful waiting, resection reduces the risk of death by 8%.

The **relative risk reduction (RRR)** is the absolute risk difference expressed as a percentage of the risk of the control or untreated group. Again, using the above example:

The relative risk reduction in mortality from prostate cancer attributable to prostate resection is 53% (8% ÷ 15% = 0.533).

Odds

An **odds** is the probability of an event happening divided by the probability of it *not* happening. Odds is not the same as risk:

The risk (or probability or frequency) of drawing a heart from a deck of 52 cards is 13 ÷ 52 = 1/4 = 25%.

The odds of drawing a heart is the probability of drawing a heart divided by the probability of not drawing a heart: 13 ÷ 39 = 1/3 = 33%.

For uncommon outcomes, the odds and risk are similar. For example, the risk of drawing a face card from a deck is 12 ÷ 52, or about 0.23, whereas the odds are 12 ÷ 40, or about 0.30, not that much different from 0.23. For common outcomes, the odds will be higher than the risk: the risk of drawing a card with an even number (not counting face cards) is 20 ÷ 52, or about 39%, but the odds are 20 ÷ 32, or 63%, which is nowhere near the 39%.

In a clinical trial, the odds of death with watchful waiting was 0.18 (30 of 200 men who died ÷ 170 men who did not die) and with resection, 0.08 (14 of 200 men who died ÷ 186 men who did not die).

Odds (and odds ratios) are hard to understand, but they are necessary in retrospective studies and are the output

of logistic regression analyses, which is a particularly useful statistical method.

Hazards

A **hazard rate** is an incidence rate: the number of new events per population at-risk per unit time. More precisely, a hazard is the “instantaneous event rate,” or the probability that if an event has not occurred in one period, it will occur in the next. Notice that a hazard is a *rate* (the number of new events of disease per population at-risk *per unit time*; here, a year), whereas incidence is the *proportion* of new cases occurring *over a given period with many units of time*; that is, over several years vs. per year.

The hazard rate for death after radical prostatectomy was 0.4% at 5 years, 0.7% at 10 years, and 1% at 15 years.

Hazards rates are seen in time-to-event studies with binary (only two) outcomes, often alive or dead. They are the output of Cox proportional hazards regression analyses, which can also be used to identify which factors are associated with living or dying. They are also often indicated on Kaplan-Meier or survival curves, which show the incidence (death) rate at any given time in a study.

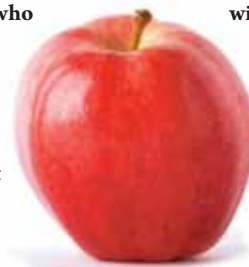
Measures of association

The association between two groups can be determined by dividing the value of a measure of risk in one group by that in another. The result is a ratio – a risk ratio, odds ratio, or hazards ratio. If the risk (or odds or hazards) is the same in the two groups, the ratio will be 1. By convention, risks greater than 1 are considered to be harmful or more common in one group than in the other, and those less than 1 are considered to be protective or less common than in the other.

Risk ratios

A **risk ratio** or **relative risk** is simply a ratio of two risks (Box 1).

The risk ratio of death from prostate cancer with watchful waiting is 2.14 (15% ÷ 7% = 2.14); men who choose watchful waiting over prostate resection are 2 times as likely to die from the disease as those who choose resection.



Because the risk ratio is the risk of one group divided by another, it matters which group is in the numerator and which is in the denominator: **If the risk ratio is 2, the risk for one group is 2 times (200%) as likely as it is for the other. If the risk ratio is 0.5, the risk for one group is half (50%) the risk of the other.**

Here, both ratios indicate that the risk in one group is twice as great as the risk in the other. Thus, by convention, protective factors are described with ratios of less than 1, and harmful factors are described with ratios of greater than 1.

Relative risk is not the same as the relative risk reduction. The relative risk is a ratio of two risks, whereas the relative risk reduction is the absolute risk reduction expressed as a percentage of the risk in the control group.

Odds ratios

The **odds ratio** is the odds for one group divided by that for another (Box 2). In the example, the *odds* of smokers having heart attacks is the number of smokers with heart attacks divided by *the number of smokers who did not have heart attacks*: $14 \div 22 = 0.636$. The odds of non-smokers having heart attacks is: $5 \div 33$, or 0.152. The odds ratio is: $0.636 \div 0.152 = 4.2$, which means that the odds of smokers having a heart attack are 4.2 times as high as that of non-smokers.

To continue with the example of prostate cancer:

The odds ratio of dying with watchful waiting is 2.3 ($17.6 \div 7.5$).

Hazards ratios

A **hazard ratio** is a risk ratio or a ratio of *incidence rates*. (In contrast, odds ratios and risk ratios are ratios of *proportions*.)

Hazards ratios are found in time-to-event studies with binary outcomes (lived or died; cured or not) and are the output of Cox proportional hazards regression, which is used in “time-to-event” or survival analysis. (However, “survival” is not the endpoint, death is. “Time-to-event analysis” is thus the most accurate and preferred term.) Importantly, the outcome of time-to-the-event analysis is not the event itself, it is the *time* from a given starting point to the time when the event occurred. For example, the time between hospitalisation and death is what we are interested in, not in the death itself.

Prospective cohort studies: risks and hazards

Risk and risk ratios

In a cohort study, exposure is assessed before the outcome is measured. We assemble a sample of people who have the same characteristics of interest and follow them forward in time, looking for a specified outcome. For example, we could enroll a cohort of currently healthy people, record their exercise habits over several years, and wait to see which ones will have a heart attack. Because all participants were healthy at the beginning of the study, we can calculate the risks and risk ratios of heart attacks; we know “how many cards” we are starting with.

Hazards and hazards ratios

As with risk and risk ratios, we can use hazards and hazards ratios in prospective or cohort studies. The difference is that we can now determine the incidence of heart attack not only over the entire period of the study but for any given time in the study. That is, with risks, we are counting *the number of heart attacks* during the study period and dividing that number by the number of participants at risk for heart attack during the period. With hazards, we are collecting data on the *time* between the beginning of the study and each heart attack during the study. The hazards ratio gives us the average risk of having a heart attack at any given time during the study. We can also graph this “hazards function” as a Kaplan-Meier or survival curve.

Retrospective case-control studies: odds

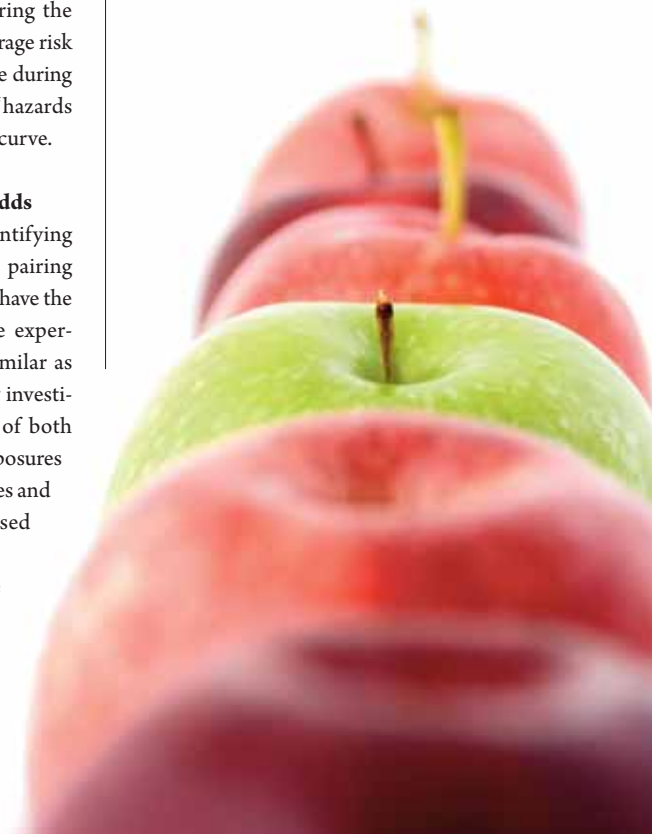
Case-control studies begin by identifying patients with a diagnosis (the cases), pairing them with a group of people who do not have the diagnosis but who otherwise have life experiences or personal characteristics as similar as possible to the cases (the controls). By investigating the history and characteristics of both groups, investigators hope to identify exposures or characteristics that differ between cases and controls. That is, outcomes are assessed before exposures.

Whereas risk and risk ratios are appropriate for prospective studies, odds and odds ratios are appropriate in retrospective studies. To continue the above example with playing cards, when we calculated the risk of drawing a heart, we knew how many cards were in the deck. In a prospective study, we

know our sample has not yet experienced the event of interest, so the sample size is essentially “the number of cards in the deck.”

In a retrospective study, however, we are starting with the event and looking back in time to find exposures that might be associated with the event. Thus, we don’t know how many people *might* have been at risk for the exposure or the event: we don’t know how many cards are in the deck, so to speak. We do know how many cases and controls we chose. That is, we can calculate the odds of the exposure for each group and compare the groups with the odds ratio (Figure 1).

Relative risk is not the same as the relative risk reduction. The relative risk is a ratio of two risks, whereas the relative risk reduction is the absolute risk reduction expressed as a percentage of the risk in the control group.



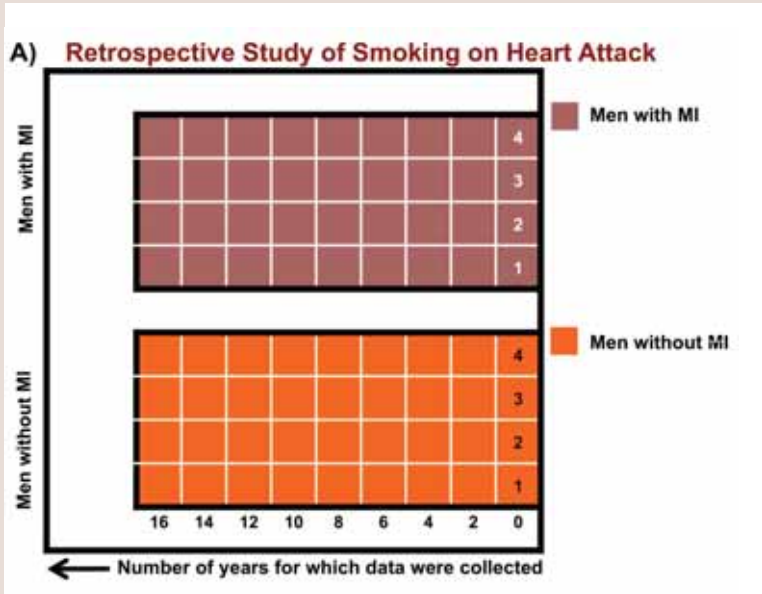
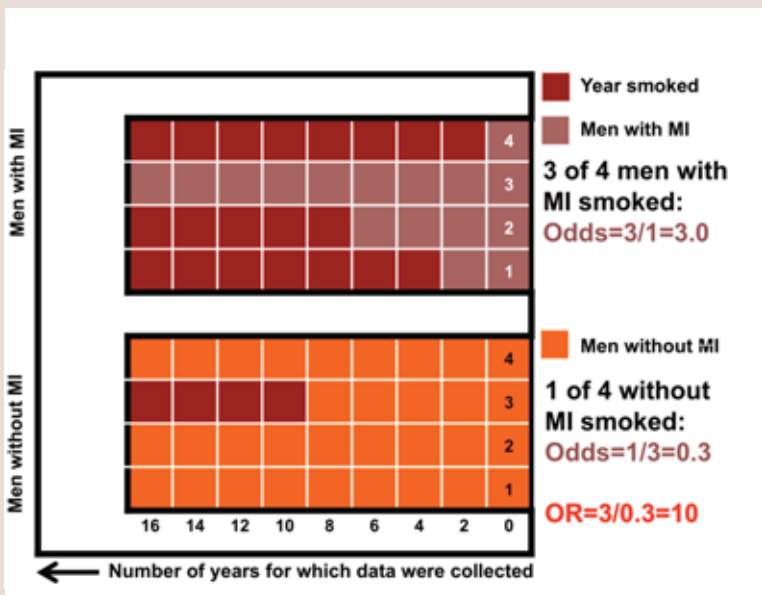


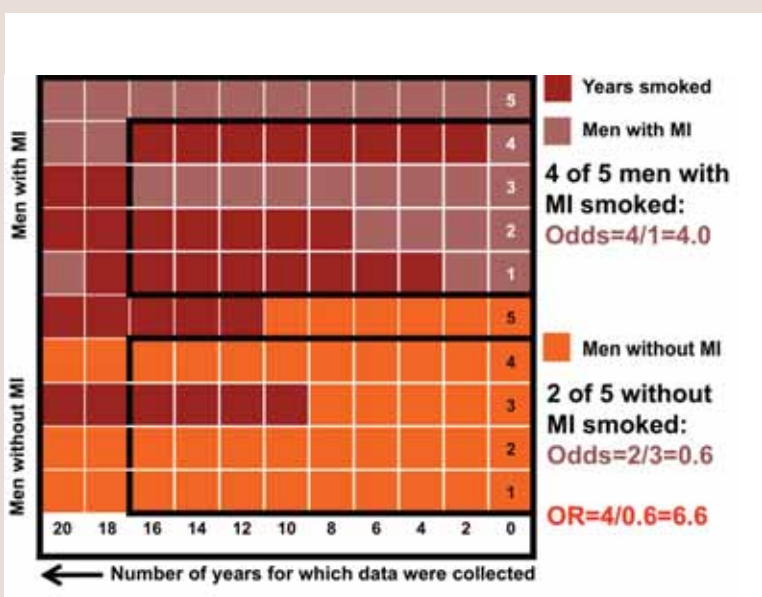
Figure 1. Odds and odds ratios: Example from a retrospective study on myocardial infarction (MI).

Odds and odds ratios are valuable in case-control studies because the true number of people at risk for the event is unknown. Thus, decisions about how many people to study and how far back in time to go may affect the results of the study.

(A) A planned case-control study for determining the association between smoking and heart attack. The 4 cases are men with heart attacks, and the 4 controls are men without heart attacks who have been matched with the cases on relevant criteria, such as age, occupation, and education. The study is looking for smoking behaviour over the past 16 years.



(B) The study as conducted revealed that 3 of the 4 cases and 1 of the 4 controls smoked at least some time during the study period. Thus, the odds of a heart attack among cases is $3 \div 1$, or 3.0, and that for controls is $1 \div 3$, or 0.3. The odds of cases having a heart attack were 10 times as great as that of the controls.



(C) The study as conducted was based on the decisions by the researchers to study 4 cases and 4 controls over 16 years. Had they chosen to study 5 cases and 5 controls over 20 years, the results would have been different: the odds ratio would have been 6.6, not 10.

Box 1. Calculating risk and the risk ratio

Risk is the number of people in whom an event happened divided by the number of people in whom the event could happen. When calculating risk, the total number of people in each group (here, smokers and non-smokers) is the denominator. If these data were collected in a cross-sectional study, the term “prevalence risk ratio” might be used instead.

Smoking Status	Heart Attack	No Heart Attack	Total
Smokers	14	22	36
Non-smokers	5	33	38
Total	19	55	74

The risk of heart attack among smokers: $14 \div 36 = 0.39$
 The risk of heart attack among non-smokers: $5 \div 38 = 0.13$
 The risk ratio is $0.39 \div 0.13 = 3$
 The risk of smokers having a heart attack is 3 times as high as that of non-smokers.

Box 2. Calculating odds and odds ratio

Odds is the probability of an event happening divided by the probability that it did not happen. If these data were collected in a cross-sectional study, the term prevalence odds ratio might be used instead.

Smoking Status	Heart Attack	No Heart Attack	Total
Smokers	14	22	36
Non smokers	5	33	38
Total	19	55	74

The odds of heart attack among smokers: $14 \div 22 = 0.636$
 The odds of heart attack among non-smokers: $5 \div 33 = 0.152$
 The odds ratio: $0.636 \div 0.152 = 4.2$
 The odds of smokers having a heart attack is 4.2 times as high as that of non-smokers.
^a The odds ratio can also be calculated as the “cross-product”:
 $(14 \times 33) \div (5 \times 22) = 4.2$

Box 3. Various measures of the risk of death from prostate calculated from the same data

Absolute risks should always be reported because all other measures can be calculated from them. Natural frequencies are probably the most easily understood.

Measure	Value
Absolute risk with watchful waiting	15%
Absolute risk with resection	7%
Absolute risk reduction with resection	8%
Risk ratio for watchful waiting	2.14
Relative risk reduction with resection	53%
Odds with watchful waiting	0.18
Odds with resection	0.08
Odds ratio with watchful waiting	2.3
10-year hazard rate with resection	0.7%
Natural frequency, watchful waiting	15 of 100 men
Natural frequency, resection	7 of 100 men

Data are from a study of men with prostate cancer in whom 14 of 200 treated with resection died and 30 of 200 treated with watchful waiting died.

Cross-sectional surveys: risks and odds

Cross-sectional studies collect data about exposures and outcomes at a single point in time. From the survey results, we can also calculate risk and odds ratios. These ratios are calculated and interpreted as above, but because the data are collected at a single point in time, they are referred to as the **prevalence risk ratio** (or simply, the **prevalence ratio**), and the **prevalence odds ratio** (Boxes 1 and 2).² Apparently, neither ratio is common in medical research.

Conclusion

Communicating risk effectively is not easy, in part because any of several measures can be reported, not all of which are easily understood (Box 3). Probably the most effective way to report risk is with **natural frequencies**, or percentages expressed in terms of 100 (or 1,000 or 10,000 people):

Of every 100 men with prostate cancer treated with watchful waiting, 15 will die.

However, whereas the mathematical aspects of risks are pretty straight forward, the psychological aspects are far more important and often counter to reality. We are more afraid of flying than of driving, despite the fact that flying is by far the safer way to travel. And that is a subject that must wait for a different article.

Conflicts of interest

I am the author of one of the two references cited.

References

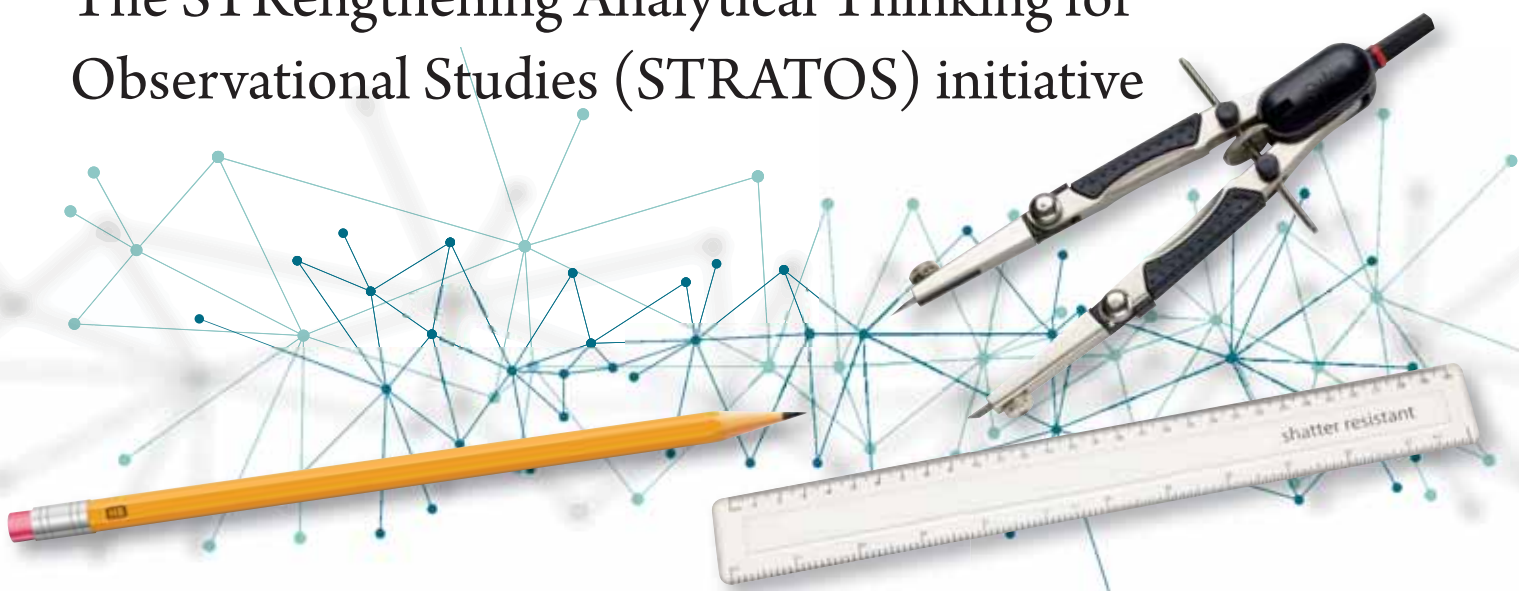
- Lang TA, Sacci M. How to report statistics in medicine: Annotated guidelines for authors, editors, and reviewers. Philadelphia: American College of Physicians, second edition, 2006.
- Alexander LK, Lopes B, Ricchetti-Masterson K, Yeasts KB. Cross-sectional studies. In: Epidemiologic Research and Information Center (ERIC) notebook second edition, #8. University of North Carolina Chappel Hill Department of Epidemiology. Available from: https://sph.unc.edu/files/2015/07/nciph_ERIC8.pdf. Accessed May 13, 2017.

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Guidance for designing and analysing observational studies:

The STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative



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Abstract

Observational studies pose a number of biostatistical challenges. Methodological approaches have grown exponentially, but most are rarely applied in the real world. The STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative is an international collaboration that was formed to provide guidance to help bridge the gap between methodological innovation and application. STRATOS is focused on identifying issues and promising approaches for planning and analysing observational studies. Crucially, STRATOS will communicate its findings to a wide audience with different levels of statistical knowledge. In this article, we provide an example illustrating the need for such guidance and describe the structure, general approach, and general outlook of the STRATOS initiative.

Introduction

Substantial progress has been made in the methodology of clinical and epidemiological studies over the past few decades. However, research quality in the health sciences has not always matched this progress. Altman expressed several critical concerns in an editorial titled “The scandal of poor medical research”,¹ and Ioannidis argued that most published research findings are

false.² In 2014, *The Lancet* started a series called “Research: Increasing Value, Reducing Waste”.³ The question is no longer whether medical science needs to change but rather “How should medical science change?”⁴ An estimated 85% of research investment is wasted.⁵ A substantial part of this is due to weaknesses in the design, analysis, and reporting of medical research.⁶ For studies on prognostic factors, Sauerbrei described several deficiencies and illustrated weaknesses and false conclusions that may arise from the use of inappropriate statistical methods in data analysis.⁷

Problems with the quality of medical research and the importance of using accurate statistical methodology are also discussed outside the medical literature. In the article “Unreliable research: Trouble at the lab”,⁸ the *Economist* summarised the current situation:

Scientists’ grasp of statistics has not kept pace with the development of complex mathematical techniques for crunching data. Some scientists use inappropriate techniques because those are the ones they feel comfortable with; others latch on to new ones without understanding their subtleties. Some just rely on the methods built into their software, even if they don’t understand them.

Pointing to insufficient education of many researchers who attempt to use advanced statistical packages, Vickers⁹ recently argued that

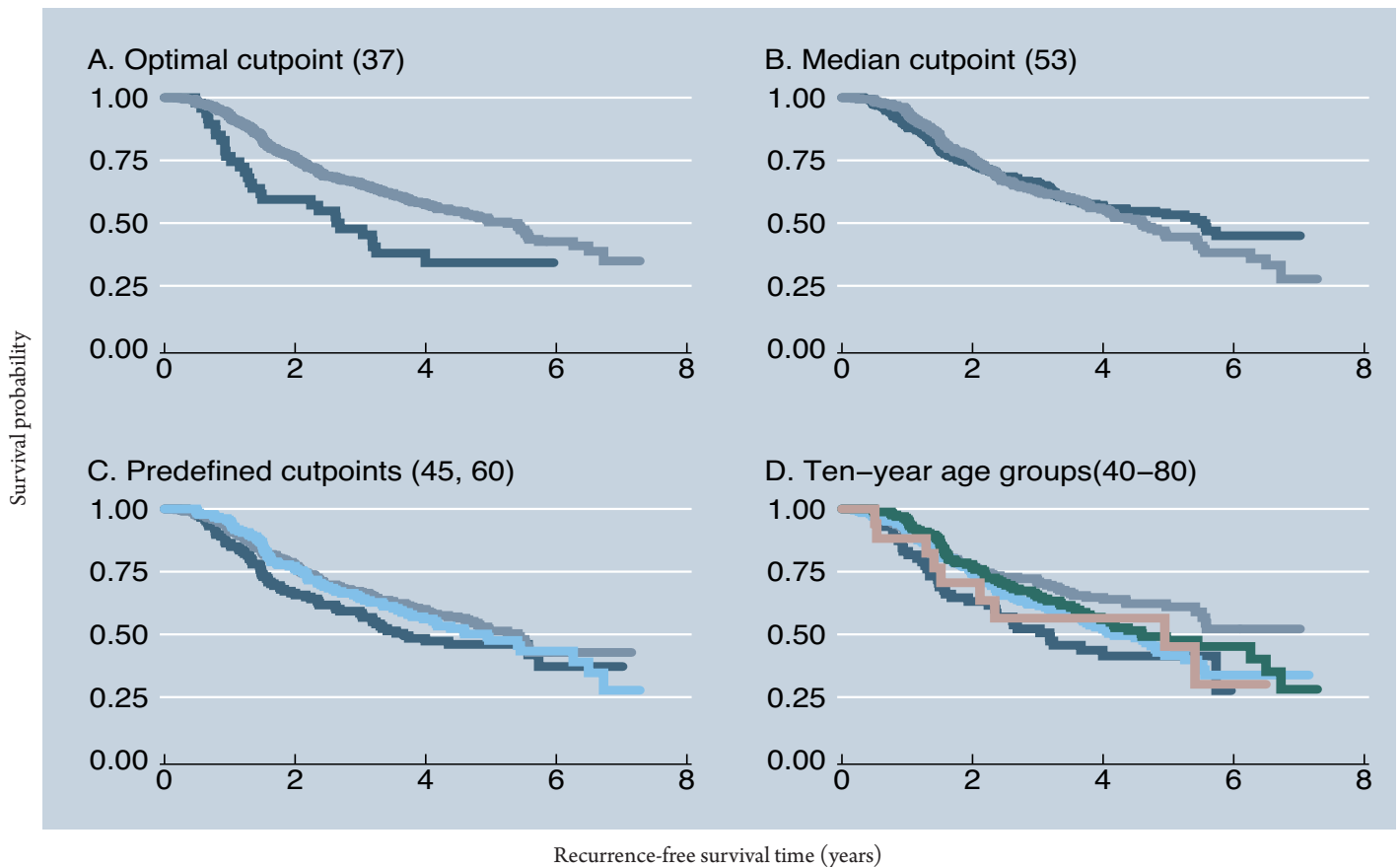


Figure 1. Kaplan-Meier plots using four alternative methods of categorizing age

(A) “Optimal” cutpoint (≤ 37 vs > 37 years). (B) Cutpoint based on the median (≤ 53 vs > 53 years). (C) Cutpoints predefined from earlier analyses and based on menopause ($\leq 45, 46$ to $60, > 60$ years); (D) 10-year increments ($\leq 40; 41-50; 51-60; 61-70; > 70$). In all panels, the youngest age group is indicated in dark blue.

A mistake in the operating room can threaten the life of one patient; a mistake in statistical analysis or interpretation can lead to hundreds of early deaths. So it is perhaps odd that, while we allow a doctor to conduct surgery only after years of training, we give SPSS to almost anyone.

In this article, we present the STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative,¹⁰ which is intended to develop guidance for planning and analysing observational studies. Below, we provide an example of difficulties in selecting an appropriate statistical method, which illustrates the need for such guidance.

Difficulties in selecting an appropriate statistical method: the example of handling one continuous variable

In medicine, continuous measurements, such as age, weight, and blood pressure, are often used to assess risk, predict outcome, or select a therapy. Background knowledge or the type of question can strongly influence how continuous variables are used, but the method for analysing contin-

uous variables must often be selected.

Continuous variables are commonly assumed to be linearly related to outcome, but this is often inappropriate. To avoid this assumption, cutpoints are often applied to categorise the variable, implying regression models with step functions. At first glance, this seems to simplify analysis and aid interpretation, but categorising discards information and raises critical issues, such as how many cutpoints to use and where to place them. In addition, cutpoints create biologically implausible step functions, whereby individuals above and below a cutpoint have different risks – which is nonsensical.^{1,11,12}

Consider the prognostic effect of age on recurrence-free survival (RFS) in breast cancer patients, an example discussed in detail in “Continuous variables: to categorise or to model” by Sauerbrei and Royston¹³ and using data from a study by the German Breast Cancer Study Group. The data are publicly available and further details about the study have been published.¹⁴ To analyse the impact of age on RFS, age categories can be set using various strategies. For this analysis, we present the four options: (1) an “optimal” cutpoint to create two

groups; (2) the median as the cutpoint for two groups; (3) three groups based on a menopausal criterion; and (4) 10-year increments.

An “optimal” cutpoint of 37 years results in a large difference in survival curves between two groups: Younger patients have much lower RFS probabilities than older patients (Figure 1A). The corresponding hazard ratio estimate (Cox model) for older patients is 0.54 (95% confidence interval 0.37, 0.80). The difference in RFS between the two age groups disappears if the cutpoint is taken at the median (53 years) as indicated by a hazard ratio of 1.1 (95% confidence interval 0.88, 1.39) (Figure 1B). When age is divided into three groups according to predefined cutpoints of 45 and 60 years (premenopausal, mix, and postmenopausal), RFS differences again are small (Figure 1C). Finally, when ages are split into five 10-year age groups starting at 40 years, the probability of RFS appears slightly lower for patients under 40 years of age, with only negligible differences between the other groups, revealing that age is not linearly related to RFS (Figure 1D).

Thus, using cutpoints can lead to different and inconsistent results, even when only one

variable is considered.¹ An alternative and more appropriate approach is to estimate the functional form of a continuous variable on the outcome, for example using spline-based approaches or fractional polynomials. In contrast to cutpoint approaches, splines and fractional polynomials use the full information from a continuous variable and have several advantages.^{10,11} In the breast cancer example, the fractional polynomial approach clearly showed that age has a strong nonlinear effect on RFS. For young patients (about 30 years of age), the relative risk of an event is high. The relative risk rapidly decreases with age, and for patients aged 40 or more years, age has a negligible influence on RFS.¹³ Because there is no widely accepted agreement about how to handle continuous variables, many analysts proceed with cutpoint approaches. Indeed, introductory graduate-level courses often encourage this. Guidance that includes evidence of the advantages and disadvantages of competing strategies is thus needed.

The trickle-down effect of using cutpoints

Using multiple strategies for cutpoints in individual studies complicates assessing the risk or prognostic effect of a continuous variable in a meta-analysis. Altman et al. (1994) found 19 different cutpoints used in the literature to categorise S-phase fraction as a prognostic factor in breast cancer.¹ Conducting a meta-analysis to compare low vs. high S-phase fraction values could be done but cannot be interpreted because a patient with a specific S-phase fraction value could belong to the “low” group in one study and the “high” group in another, depending on the cutpoint chosen.

In a review on P53 as prognostic factor for bladder cancer, Malats et al. found cut-off values

ranging between 1% and 75% to define nuclear overexpression.¹⁵ Accordingly, they concluded: “That a decade of research on P53 and bladder cancer has not placed us in a better position to draw conclusions relevant to the clinical management of patients is frustrating.”

Thus, forcing cutpoints to fit the data may not only lead to misleading conclusions but may also reduce the usefulness of the results for making clinical decisions. Obviously, in observational studies, several factors can influence the outcome, and a multivariable analysis would be needed. In addition to investigating the functional form for a continuous variable, the researcher must decide which other variables to include in the statistical model. For the breast cancer example, see Sauerbrei and Royston¹³ for more detail, and for background and basic issues for interpreting and reporting results from multivariable analyses, refer to Valveny and Gilliver.¹⁶

Typical weaknesses of statistical analyses

Our example illustrated only one serious problem in statistical analysis. Many other weaknesses have been identified, including:¹⁰

- inappropriate or inefficient study design
- inappropriate, inefficient, or outdated choice of statistical methods
- misapplication of a valid method
- interpretation problems, including misinterpretation of *P* values, over-confidence in results, misleading interpretation of parameter estimates, bias, and confounding
- reporting problems, including inadequate details for methods and results

Although some methodological errors relate to the failure to grasp some complex or subtle statistical issues, problems in applying even

simple methods are widespread (for further details and examples, see Sauerbrei et al.¹⁰ and Lang and Altman¹⁷).

The need for guidance in planning and analysing observational studies

During the last two decades, several initiatives have been started with the goal of improving research in the health sciences. Transparent and complete reporting is a prerequisite for judging the usefulness of data and interpreting study results in an appropriate context. Reporting guidelines have been developed for many different types of studies. These can be found on the EQUATOR network website (www.equator-network.org/), which serves as a repository of these guidelines and assists in the development of reporting guidelines.¹⁸ The STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) statement provides excellent guidelines for reporting observational studies,¹⁹ and the guiding principles for reporting statistical methods and results were recently published.¹⁷

Because of the problems in analysing observational studies, guidance on the advantages and disadvantages of competing statistical strategies is needed.¹⁰ For various reasons, this is much more difficult than generating reporting guidelines. In addition, suitable guidance must be tailored to the experience and statistical knowledge of the user, which can vary widely.

The STRATOS initiative

Understanding and overcoming the formidable challenges in designing and analysing observational studies requires a broad-based,

Table 1. Topic groups and their chairs

Topic Groups	Chairs
1 Missing data	James Carpenter (UK), Katherine Lee (Australia)
2 Selection of variables and functional forms in multivariable analysis	Michal Abrahamowicz (Canada), Aris Perperoglou (UK), Willi Sauerbrei (Germany)
3 Initial data analysis	Marianne Huebner (USA), Saskia le Cessie (Netherlands), Werner Vach (Germany)
4 Measurement error and misclassification	Laurence Freedman (Israel), Victor Kipnis (USA)
5 Study design	Suzanne Cadarette (Canada), Mitchell Gail (USA)
6 Evaluating diagnostic tests and prediction models	Gary Collins (UK), Carl Moons (Netherlands), Ewout Steyerberg (Netherlands)
7 Causal inference	Els Goetghebeur (Belgium), Ingeborg Waernbaum (Sweden)
8 Survival analysis	Michal Abrahamowicz (Canada), Per Kragh Andersen (Denmark), Terry Therneau (USA)
9 High-dimensional data	Lisa McShane (USA), Joerg Rahnenfuehrer (Germany)

international group of statistical experts who are also involved with real-world applications. This is the driving vision behind the STRATOS initiative (<http://www.stratos-initiative.org>), which was launched in 2013 at the 34th conference of the International Society of Clinical Biostatistics (ISCB).¹⁰ STRATOS remains affiliated with the society and had dedicated sessions or mini-symposia at each annual meeting from 2013 to 2016.

STRATOS brings together methodological researchers in several areas of statistics essential for analysing observational studies. These experts have largely complementary knowledge, which allows STRATOS to address complex challenges in the design and analysis of observational studies. STRATOS works to develop, validate, and compare state-of-the-art methods for topics relevant to many kinds of statistical analyses.

Because there is a finite pool of experienced statisticians, many analyses are conducted by researchers with limited statistical literacy and experience. Consequently, the ultimate objective of the STRATOS initiative is to develop guidance for data analysts and researchers with different levels of statistical training, skills, and experience. The initiative considers three levels of statistical knowledge: low (level 1), experienced (level 2), and expert in a specific area (level 3).

Our initial goal is to develop guidance for experienced statisticians (level 2), which involves drafting reviews of methods used in the literature and providing empirical evidence to assess and compare approaches, with the goal of providing arguments for state-of-the-art methodology.

The guidance is informed by a recent list of recommendations for how to improve the uptake of novel methods.²⁰ It will cover practical issues such as potential pitfalls of inappropriately using

“conventional” methods; criteria for choosing appropriate, validated methods that can overcome specific challenges; and software for implementing these advanced methods. The level 2 guidance will then be adapted to researchers with weaker statistical knowledge, which includes most clinicians and medical students (level 1), while experts in specific areas (level 3) will work to identify current gaps in knowledge and improve, validate, and compare existing methods.

STRATOS currently has nine topic groups (TGs) (Table 1), all of which include 8 to 12 members. Further details are available in Sauerbrei et al 2014¹⁰ and on the STRATOS website. Ten cross-cutting panels have been created to coordinate the activities of different TGs, share best research practices, and disseminate research tools and results across TGs (Table 2). These panels address common issues such as creating a glossary of statistical terms, giving advice on how to conduct simulation studies, and setting publication policies for the initiative. The recommendations of the cross-cutting panels are intended to support, integrate, and harmonise work within and across the TGs and to increase transparency in producing guidance. Interested colleagues can apply to become a member of one or two TGs or panels at <http://www.stratos-initiative.org>.

Summary and outlook

Although substantial progress has been made in designing and analysing data from clinical and epidemiological studies, real-world application lags far behind the advances. This is largely because most researchers have limited knowledge and experience in using advanced statistical methods and software, and even experts can

disagree on how best to analyse complex study data, with no consensus on “state-of-the-art” methodology. The STRATOS initiative aims to fill this gap by developing guidance and tools for applying statistical methods for observational research. This is an important step in improving evidence-based decision-making about healthcare.

The STRATOS initiative began in 2013 with about 40 members and, despite a lack of specific funding, has grown to more than 80 members from 16 countries in 2017. Work, research, discussions, and activities are ongoing in nine key relevant areas. Much research, in particular simulation studies, is needed to assess competing statistical approaches. STRATOS’s structure is designed to make the resulting guidance broadly useful, but collaboration with clinicians, applied researchers, scientific societies, and related projects and initiatives is needed.

The emergence of “big data” is an additional driver for STRATOS. Big data pose particular challenges and opportunities, and it encompasses diverse areas and data sources. Because of this complexity, STRATOS has decided not to have a big data topic group but instead to encourage all TGs to consider it in their work.

To improve statistical methodology and its transparency, statistical researchers must put more emphasis on comparing competing strategies and must generate evidence to support state-of-the-art methodologies. They must also provide guidance that is appropriate for the large community of people who analyse and consume data, who have a wide range of statistical knowledge and experience.

If you are interested in the work of the STRATOS initiative or would like to participate, please visit us at <http://www.stratos-initiative.org/>.

Table 2. Panels, their chairs, and co-chairs

Panels	Chairs and Co-Chairs
Membership	James Carpenter (UK), Willi Sauerbrei (Germany)
Publications	Bianca De Stavola (UK), Mitchell Gail (USA), Petra Macaskill (Australia), Stephen Walter (Canada)
Website	Joerg Rahnenfuehrer (Germany), Willi Sauerbrei (Germany)
Glossary	Simon Day (UK), Marianne Huebner (USA), Jim Slattery (UK)
Simulation Studies	Michal Abrahamowicz (Canada), Harald Binder (Germany)
Contact Organisations	Douglas Altman (UK), Willi Sauerbrei (Germany)
Literature Review	Gary Collins (UK), Carl Moons (Netherlands)
Data Sets	Hermann Huss (Germany), Saskia Le Cessie (Netherlands), Aris Perperoglou (UK)
Knowledge Translation	Suzanne Cadarette (Canada), Catherine Quantin (France)
Bibliography	To be determined



Conflicts of Interest and Disclaimers

The authors declare no conflicts of interest.

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References

1. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using “Optimal” cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst* 1994;86:829–35.
2. Ioannidis JP. Why most published research findings are false. *PloS Med* 2005;2:E124.
3. The Lancet. Research: increasing value, reducing waste [series]. 2014. Available from: www.thelancet.com/series/research.
4. Kleinert S, Horton R. How should medical science change? *Lancet* 2014; 383:197–198.
5. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009;374:86–9.
6. Ioannidis JP, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014;383: 166–175.
7. Sauerbrei W. Prognostic factors – confusion caused by bad quality of design, analysis and reporting of many studies. In Bier H, editor. *Current research in head and neck cancer. Advances in oto-rhino-laryngology*. Basel, Karger 2005;62:184–200.
8. Trouble at the lab. *The Economist* 2013 Oct 18.
9. Vickers A. Interpreting data from randomized trials: the Scandinavian prostatectomy study illustrates two common errors. *Nat Clin Pract Urol* 2005;2:404–5.
10. Sauerbrei W, Abrahamowicz M, Altman DG, le Cessie S and Carpenter J on behalf of the STRATOS initiative. STREngthening Analytical Thinking for Observational Studies: the STRATOS initiative. *Stat Med* 2014;33:5413–32.
11. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006;25:127–41.
12. Van Walraven C, Hart RG. Leave ‘em alone – why continuous variables should be analyzed as such. *Neuroepidemiology* 2008;30:138–9.
13. Sauerbrei W, Royston P. Continuous Variables: To categorize or to model? In: Reading C, editor. *The 8th International Conference on Teaching Statistics – Data and Context in statistics education: Towards an evidence based society*. International Statistical Institute, Voorburg. 2010.
14. Royston P, Sauerbrei W. *Multivariable model-building – a pragmatic approach to regression analysis based on fractional polynomials for modelling continuous variables*. Wiley, Chichester 2008.
15. Malats N, Bustos A, Nascimento CM, Fernandez F, Rivas M, Puente D et al. P53 as a prognostic marker for bladder cancer: a meta-analysis and review. *Lancet Oncol* 2005;6:678–86.
16. Valveny N, Gilliver S. How to interpret and report the results from multivariable analyses. *Med Writ* 2016;25:37–42.
17. Lang TA, Altman DG. Statistical analyses and methods in the published literature: The SAMPL guidelines. *Med Writ* 2016; 25:31–5.
18. Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. *BMC Med* 2010;8:24.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandenbroucke JP for the STROBE initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology* 2007;18:800–4.
20. Cadarette SM, Ban JK, Consiglio GP et al. Diffusion of innovations model helps interpret the comparative uptake of two methodological innovations: co-authorship network analysis and recommendations for the integration of novel methods in practice. *J Clin Epidemiol* 2017; 84:150–60.

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Guidelines for disclosing the results from observational trials

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Abstract

Observational trials are a relevant part of clinical research. Publishing their results can be challenging for scientists and writers. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was the first guideline developed to identify the minimal information that should be included in articles reporting observational and epidemiological research. More than 50 ancillary guidelines tailored to specific needs are now available to assist authors in preparing successful articles on observational studies.

Introduction

In observational studies (OSs), the researcher collects information on the attributes or measurement of interest but does not influence events. OSs include surveys and most epidemiological studies, and they can be prospective or retrospective. Many OSs are carried out to investigate possible associations between various factors and the development of a disease or condition. In general, OSs are used to investigate factors or exposures that cannot be controlled by the investigators, such as jobs or smoking habits.¹

Randomised controlled trials (RCTs) are widely considered as the "gold standard" in



research; nevertheless, they have several limitations. In some cases, RCTs can be unnecessary, inappropriate, impossible, or inadequate.² Moreover, researchers can now answer many questions using the enormous amount of clinical data that have become available through registries and other powerful digital platforms.³ This has become increasingly important as research and development costs grow and budgets decrease. OSs also play an important role in identifying the benefits and harms of medical interventions in ways that RCTs cannot. For example, OSs are more suitable for detecting rare or late adverse effects of treatments, and they can help show what is achieved in daily medical practice.⁴

Publications based on OSs, however, often lack critical information or are unclear due to insufficient reporting of potential confounding variables,⁵ methods used for identifying cases and controls,⁶ and eligibility criteria.⁷ Reporting guidelines have therefore been developed for OSs.

The STROBE Statement

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was developed to provide researchers with an appropriate tool to improve reporting of

OSs.⁸ STROBE was the first guideline especially designed for OSs and can be applied to any study type, although many additional guidelines are now available for more specific observational study designs.

History of STROBE

The first reporting guideline for researchers was the Consolidated Standards of Reporting Trials (CONSORT) Statement, developed in 1996 and revised 5 years later.^{9,10} It helped improve the quality of reports from RCTs. Similar initiatives have followed for different studies, such as diagnostic studies and OSs. STROBE was created by a network of methodologists, researchers, and journal editors who met in 2004 to develop recommendations for the reporting of OSs. STROBE contains recommendations on the minimal information to be included in an accurate and complete article for the three main OSS designs: cohort, case-control, and cross-sectional.⁴ The STROBE statement was published in eight journals and was accompanied by simultaneous publication of an explanation and elaboration article in three journals.⁸

The STROBE checklist

The STROBE Statement includes a checklist of 22 items that should be addressed in articles

Table 1. The STROBE checklist

Section	Item No.	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) <i>Cohort study</i> – Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		<i>Case-control study</i> – Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		<i>Cross-sectional study</i> – Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	(b) <i>Cohort study</i> – For matched studies, give matching criteria and number of exposed and unexposed
		<i>Case-control study</i> – For matched studies, give matching criteria and the number of controls per case
		Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe measurement comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) <i>Cohort study</i> –If applicable, explain how loss to follow-up was addressed
		<i>Case-control study</i> –If applicable, explain how matching of cases and controls was addressed
Participants	13*	<i>Cross-sectional study</i> –If applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses
		(a) Report numbers of individuals at each stage of study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
Descriptive data	14*	(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
		(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
Outcome data	15*	(b) Indicate number of participants with missing data for each variable of interest
		(c) <i>Cohort study</i> – Summarise follow-up time (e.g. average and total amount)
		<i>Cohort study</i> – Report numbers of outcome events or summary measures over time
Main results	16	<i>Case-control study</i> –Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> –Report numbers of outcome events or summary measures
		(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
Other analyses	17	(b) Report category boundaries when continuous variables were categorised
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
		Report other analyses done –e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

reporting OSs (Table 1). The checklist was intended to provide guidance on reporting OSs but does not provide guidance on designing or conducting them. The checklist is also not designed as an instrument for evaluating the quality of OSs.

The 22 items in the STROBE checklist relate to what should be included and how in the different sections of the article, from title and abstract to discussion section. An item for study funding is also included. Of the 22 items in the checklist, 18 are common to all three main observational study designs. The remaining four are specific to the study design, and different versions for all or part of the item are provided. For some items, information should be provided separately for cases and controls in case-control studies or for exposed and unexposed groups in cohort and cross-sectional studies. Although presented here as a single checklist, separate checklists are available.

Website

The STROBE checklist and other related documents are available at the site for the STROBE Statement (www.strobe-statement.org). Included on the website are lists of journals where the statement and the explanatory paper were published, journals that refer to the STROBE Statement in their instructions for authors, and members of the STROBE group. The website contains the original English version of the STROBE statement and translations in eight other languages.¹¹

Addenda to the STROBE Statement and other related guidance

Although the STROBE statement was designed to cover the three main types of OSs, several extensions or related guidelines have been developed for other designs or specific topic areas, such as case studies/series, genetics studies, and epidemiological studies (Table 2). Key guidelines include CARE for case reports,¹² STREGA for genomic studies,¹³ and RECORD for routinely collected health data.¹⁴

The EQUATOR Network: a tool for searching all available guidelines

The EQUATOR Network (www.equator-network.org) is an international initiative started in 2006 that consolidates reporting

guidelines. Its goal is to improve the reliability and value of published research by promoting transparent and accurate reporting through the use of reporting guidelines. Although Table 2 contains an up-to-date list, new guidelines continue to be developed, so the best way to find the right guidelines is to use the search function, available at www.equator-network.org/reporting-guidelines/ and depicted in Figure 1.

OS reporting guidelines under development

As summarised on the EQUATOR Network website (www.equator-network.org/library/reporting-guidelines-under-development/), several guidelines are under development in other areas of OSs. Importantly, they include an extension of STROBE for conference abstracts and recommendations for preparing protocols for OSs (SPIROS). Also under development are a guideline for reporting of observational epidemiology studies integrating data on humans, animals and/or vectors, and their shared environments (COHERE); a guideline specific for environmental epidemiology analyses (GREEN); guidance for reporting the long-term impact of genocide and war on mental health (GESUQ); and guidance on the psychometric properties of patient-reported outcomes.



Figure 1. The EQUATOR Network guideline search page

The search page is available at <http://www.equator-network.org/reporting-guidelines/>.

Conclusion

More than 50 guidelines are available for reporting OSs, and more are under development. These guidelines are of great help to medical writers preparing publications on OSs and should help improve their accuracy and completeness.

Disclaimers

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

Conflicts of interest

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

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Table 2. Additional guidelines for observational studies

OSS study/data type	Acronym	Full name	Reference
Case studies/series			
Case reports	CARE	Consensus-based clinical case report guideline development	12
Case series in surgery	PROCESS	Preferred reporting of case series in surgery	15
Organisational case studies	–	Developing a methodological framework for organisational case studies: a rapid review and consensus development process	16
Case series in plastic surgery	–	Designing and reporting case series in plastic surgery	17
Case series of colon and rectum tumours	–	Guidelines for reporting case series of tumours of the colon and rectum	18
Uncontrolled case series	–	Appropriate use and reporting of uncontrolled case series in the medical literature	19
Case series in acupuncture	–	Conducting and reporting case series and audits – author guidelines for acupuncture in medicine	20
Poisoning case studies	–	Guidelines for reporting case studies on extracorporeal treatments in poisonings	21
Surveys			
E-surveys	CHERRIES	Checklist for Reporting Results of Internet E-Surveys for reporting Web-based surveys	22
Surveys of clinicians	–	A guide for the design and conduct of self-administered surveys of clinicians	23
Reporting using mobile phones	mERA	Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist	24
	–	Good practice in the conduct and reporting of survey research	25
Genomics & genetics			
Genetic association	STREGA	STrengthening the REporting of Genetic Association Studies	13
Molecular epidemiology	STROBE-ME	STrengthening the Reporting of OBServational studies in Epidemiology – Molecular Epidemiology	26
Immunogenomics	–	A community standard for immunogenomic data reporting and analysis	27
Genetic risk prediction	GRIPS	Strengthening the reporting of Genetic RIsk Prediction Studies	28
Epidemiology & routinely collected data			
Kidney disease prevalence	–	Methodology used in studies reporting chronic kidney disease prevalence	29
Neuroepidemiology	STROND	Standards of Reporting of Neurological Disorders	30
Nutritional epidemiology	STROBE-nut	Strengthening the Reporting of Observational Studies in Epidemiology – Nutritional Epidemiology	31
Routinely collected health data	RECORD	The REporting of studies Conducted using Observational Routinely-collected Health Data	14
Health estimates	GATHER	Guidelines for Accurate and Transparent Health Estimates Reporting	32
Infectious diseases			
Neonatal infection	STROBE-NI	Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection	33
Antimicrobial resistance	STROBE-AMS	Recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship for epidemiologic studies focused on the link between antimicrobial-resistant bacteria and antibiotic usage	34
Molecular epidemiology of infectious diseases	STROME-ID	Strengthening the reporting of molecular epidemiology for infectious diseases	35
Nosocomial infection	ORION	Guidelines for transparent reporting of Outbreak Reports and Intervention Studies Of Nosocomial infection	36
Seroepidemiologic studies for influenza	CONSISE ROSES-I	Statement on the reporting of Seroepidemiologic Studies for Influenza	37
Rheumatology			
Drug studies in rheumatology	–	Launch of a checklist for reporting longitudinal observational drug studies in rheumatology: a EULAR extension of STROBE guidelines based on experience from biologics registries	38
Biologics registries in rheumatology	–	EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology for disclosing the results from biologics registers in in rheumatology	39

OSS study/data type	Acronym	Full name	Reference
Imaging and markers			
Magnetic resonance imaging for prostate cancer	PRECISE	Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer.	40
Magnetic resonance-targeted biopsy studies of the prostate	START	Standards of reporting for MRI-targeted biopsy studies of the prostate	41
Tumour marker prognostic studies	REMARK	REporting recommendations for tumour MARKer prognostic studies	42
Markers of cardiovascular risk	–	Criteria for evaluation of novel markers of cardiovascular risk	43
Psychiatry and heart rate variability	GRAPH	Guidelines for Reporting Articles on Psychiatry and Heart rate variability	44
Neuroimaging	–	Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration	45
Surgery & illnesses			
Medical abortion efficacy	MARE	Medical abortion reporting of efficacy	46
Intraoperative complications	CLASSIC	Definition and classification of intraoperative complications	47
Glaucoma surgery	–	A new manner of reporting pressure results after glaucoma surgery	48
Metabolic and bariatric surgery	–	Standardised outcomes reporting in metabolic and bariatric surgery	49
Emergency medicine			
Emergency department syncope risk	-	Standardised reporting guidelines for emergency department syncope risk-stratification research	50
Disaster medicine	CONFIDE	Disaster medicine reporting	51
Pain & fatigue			
Pain intensity assessment	ACTTION	Quality of pain intensity assessment reporting	52
Back pain		A consensus approach toward the standardisation of back pain definitions for use in prevalence studies	53
Chronic fatigue syndrome	–	Minimum data elements for research reports on chronic fatigue syndrome	54
Psychology & counselling			
Counselling	–	Guidelines for conducting and reporting mixed research in the field of counselling and beyond	55
Neuropsychology	–	Point and interval estimates of effect sizes for the case-controls design in neuropsychology	56
Other			
Violence risk assessment	RAGEE	Reporting guidance for violence risk assessment predictive validity studies	57
Thromboembolism	–	Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardised reporting	58
Aneurysm	–	Reporting Standards for Endovascular Repair of Saccular Intracranial Cerebral Aneurysms	59
Chinese medicine	–	Recommendations for reporting adverse drug reactions and adverse events of traditional Chinese medicine	60
Menopause	STROMA	Overview of methods used in cross-cultural comparisons of menopausal symptoms and their determinants: Strengthening the Reporting of Menopause and Ageing studies	61
End-of-life care	MORECare	Evaluating complex interventions in end of life care	62
Viscerotropic disease	–	Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunisation safety data	63
Veterinary OSs	STROBE-Vet	Methods and processes of developing the strengthening the reporting of observational studies in epidemiology	64
Health care simulation research	INSPIRE	Reporting Guidelines for Health Care Simulation Research	65
Respondent-driven sampling studies	STROBE-RDS	Strengthening the Reporting of Observational Studies in Epidemiology for Respondent-Driven Sampling Studies	66
Narratives in clinical research	–	Suggestions for improving the reporting of clinical research: the role of narrative	67
Raw clinical data	–	Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers	68
Participation in case-control studies	–	Reporting participation in case-control studies	69
Comparative safety and effectiveness research	–	Instrumental variable methods in comparative safety and effectiveness research	70

References

- Altman DG. Practical statistics for medical research. London, UK: Chapman & Hall; 1991.
- Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312:1215–8.
- Lauer MS, D'Agostino RB, Sr. The randomized registry trial – the next disruptive technology in clinical research? *N Engl J Med* 2013;369:1579–81.
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
- Pocock SJ, Collier TJ, Dandreo KJ, de Stavola BL, Goldman MB, Kalish LA et al. Issues in the reporting of epidemiological studies: a survey of recent practice. *BMJ* 2004;329:883.
- Lee W, Bindman J, Ford T, Glozier N, Moran P, Stewart R, Hotopf M. Bias in psychiatric case-control studies: literature survey. *Br J Psychiatry* 2007;190:204–9.
- Tooth L, Ware R, Bain C, Purdie DM, Dobson A. Quality of reporting of observational longitudinal research. *Am J Epidemiol* 2005;161:280–8.
- Vandenbroucke JP, von Elm E, Altman DG et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007;18:805–35.
- Golub RM, Fontanarosa PB. Researchers, readers, and reporting guidelines: writing between the lines. *JAMA* 2015; 313:1625–6.
- Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191–4.
- University of Bern. Translations of STROBE Statement. 2009 [cited 2017 Jun 2]. Available from: <https://www.strobe-statement.org/index.php?id=strobe-translations>.
- Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D. The CARE guidelines: consensus-based clinical case report guideline development. *J Clin Epidemiol* 2014;67:46–51.
- Little J, Higgins JP, Ioannidis JP et al. STrengthening the REporting of Genetic Association studies (STREGA) – an extension of the STROBE statement. *Eur J Clin Invest* 2009;39:247–66.
- Benchimol EI, Smeeth L, Guttmann A et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12:e1001885.
- Agha RA, Fowler AJ, Rajmohan S, Barai I, Orgill DP. Preferred reporting of case series in surgery; the PROCESS guidelines. *Int J Surg* 2016;36:319–23.
- Rodgers M, Thomas S, Harden M, Parker G, Street A, Eastwood A. Developing a methodological framework for organisational case studies: a rapid review and consensus development process. Southampton (UK), 2016.
- Coroneos CJ, Ignacy TA, Thoma A. Designing and reporting case series in plastic surgery. *Plast Reconstr Surg* 2011;128:361e–8e.
- Rubino M, Pragnell MVC. Guidelines for reporting case series of tumours of the colon and rectum. *Tech Coloproct* 1999;3:93–7.
- Kempen JH. Appropriate use and reporting of uncontrolled case series in the medical literature. *Am J Ophthalmol* 2011;151:7–10 e1.
- White A. Conducting and reporting case series and audits – author guidelines for acupuncture in medicine. *Acupunct Med* 2005;23:181–7.
- Lavergne V, Ouellet G, Bouchard J et al. Guidelines for reporting case studies on extracorporeal treatments in poisonings: methodology. *Semin Dial* 2014;27:407–14.
- Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *J Med Internet Res* 2004;6:e34.
- Burns KE, Duffett M, Kho ME, Meade MO, Adhikari NK, Sinuff T, Cook DJ. A guide for the design and conduct of self-administered surveys of clinicians. *CMAJ* 2008;179:245–52.
- Agarwal S, LeFevre AE, Lee J et al. Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist. *BMJ* 2016;352:i1174.
- Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. *Int J Qual Health Care* 2003;15:261–6.
- Gallo V, Egger M, McCormack V et al. STrengthening the Reporting of OBServational studies in Epidemiology – Molecular Epidemiology (STROBE-ME): an extension of the STROBE Statement. *PLoS Med* 2011;8:e1001117.
- Hollenbach JA, Mack SJ, Gourraud PA et al. A community standard for immunogenomic data reporting and analysis: proposal for a STrengthening the REporting of Immunogenomic Studies statement. *Tissue Antigens* 2011;78:333–44.
- Janssens AC, Ioannidis JP, van Duijn CM, Little J, Khoury MJ. Strengthening the reporting of genetic risk prediction studies: the GRIPS statement. *Eur J Clin Invest* 2011;41:1004–9.
- Bruck K, Jager KJ, Dounousi E et al. Methodology used in studies reporting chronic kidney disease prevalence: a systematic literature review. *Nephrol Dial Transplant* 2016;31:680.
- Bennett DA, Brayne C, Feigin VL et al. Development of the standards of reporting of neurological disorders (STROND) checklist: a guideline for the reporting of incidence and prevalence studies in neuroepidemiology. *Eur J Epidemiol* 2015;30:569–76.
- Lachat C, Hawwash D, Ocke MC et al. Strengthening the Reporting of Observational Studies in Epidemiology–Nutritional Epidemiology (STROBE–nut): An Extension of the STROBE Statement. *PLoS Med* 2016;13:e1002036.
- Stevens GA, Alkema L, Black RE et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *Lancet* 2016;388:e19–e23.
- Fitchett EJ, Seale AC, Vergnano S et al. Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI): an extension of the STROBE statement for neonatal infection research. *Lancet Infect Dis* 2016;16:e202–13.
- Tacconelli E, Cataldo MA, Paul M et al. STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. *BMJ Open* 2016;6:e010134.
- Field N, Cohen T, Struelens MJ et al. Strengthening the Reporting of Molecular Epidemiology for Infectious Diseases (STROME-ID): an extension of the STROBE statement. *Lancet Infect Dis* 2014;14:341–52.
- Stone SP, Cooper BS, Kibbler CC et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *J Antimicrob Chemother* 2007;59:833–40.

37. Horby PW, Laurie KL, Cowling BJ et al. CONSISE statement on the reporting of Seroepidemiologic Studies for influenza (ROSES-I statement): an extension of the STROBE statement. *Influenza Other Respir Viruses* 2017;11:2–14.
38. Zavada J, Dixon WG, Askling J. Launch of a checklist for reporting longitudinal observational drug studies in rheumatology: a EULAR extension of STROBE guidelines based on experience from biologics registries. *Ann Rheum Dis* 2014;73:628.
39. Dixon WG, Carmona L, Finckh A et al. EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology. *Ann Rheum Dis* 2010;69:1596–602.
40. Moore CM, Giganti F, Albertsen P et al. Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer: The PRECISE Recommendations- A Report of a European School of Oncology Task Force. *Eur Urol* 2017;71:648–55.
41. Moore CM, Kasivisvanathan V, Eggener S et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. *Eur Urol* 2013;64:544–52.
42. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. REporting recommendations for tumour MARKer prognostic studies (REMARK). *Br J Cancer* 2005;93:387–91.
43. Hlatky MA, Greenland P, Arnett DK et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. *Circulation* 2009;119:2408–16.
44. Quintana DS, Alvares GA, Heathers JA. Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): recommendations to advance research communication. *Transl Psychiatry* 2016;6:e803.
45. Wardlaw JM, Smith EE, Biessels GJ et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12:822–38.
46. Creinin MD, Chen MJ. Medical abortion reporting of efficacy: the MARE guidelines. *Contraception* 2016;94:97–103.
47. Rosenthal R, Hoffmann H, Clavien PA, Bucher HC, Dell-Kuster S. Definition and Classification of Intraoperative Complications (CLASSIC): Delphi Study and Pilot Evaluation. *World J Surg* 2015;39:1663–71.
48. Bordeianu CD, Ticu CE. A new manner of reporting pressure results after glaucoma surgery. *Clin Ophthalmol* 2012;6:23–31.
49. Brethauer SA, Kim J, el Chaar M et al. Standardized outcomes reporting in metabolic and bariatric surgery. *Surg Obes Relat Dis* 2015;11:489–506.
50. Sun BC, Thiruganasambandamoorthy V, Cruz JD. Standardized reporting guidelines for emergency department syncope risk-stratification research. *Acad Emerg Med* 2012;19:694–702.
51. Bradt DA, Aitken P. Disaster medicine reporting: the need for new guidelines and the CONFIDE statement. *Emerg Med Australas* 2010;22:483–7.
52. Smith SM, Hunsinger M, McKeown A et al. Quality of pain intensity assessment reporting: ACTTION systematic review and recommendations. *J Pain* 2015; 16:299–305.
53. Dionne CE, Dunn KM, Croft PR et al. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. *Spine (Phila Pa 1976)* 2008;33:95–103.
54. Jason LA, Unger ER, Dimitrakoff JD et al. Minimum data elements for research reports on CFS. *Brain Behav Immun* 2012;26:401–6.
55. Leech NL, Onwuegbuzie AJ. Guidelines for conducting and reporting mixed research in the field of counseling and beyond. *J Couns Dev* 2010;88:61–9.
56. Crawford JR, Garthwaite PH, Porter S. Point and interval estimates of effect sizes for the case-controls design in neuropsychology: rationale, methods, implementations, and proposed reporting standards. *Cogn Neuropsychol* 2010;27:245–60.
57. Singh JP, Yang S, Mulvey EP. Reporting guidance for violence risk assessment predictive validity studies: the RAGEE Statement. *Law Hum Behav* 2015;39:15–22.
58. Kearon C, Iorio A, Palareti G. Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. *J Thromb Haemost* 2010;8:2313–5.
59. Meyers PM, Schumacher HC, Higashida RT et al. Reporting standards for endovascular repair of saccular intracranial cerebral aneurysms. *J Neurointerv Surg* 2010;2: 312–23.
60. Wu T, Shang H, Bian Z, Zhang J, Li T, Li Y, Zhang B. Recommendations for reporting adverse drug reactions and adverse events of traditional Chinese medicine. *J Evid Based Med* 2010;3:11–7.
61. Melby MK, Sievert LL, Anderson D, Obermeyer CM. Overview of methods used in cross-cultural comparisons of menopausal symptoms and their determinants: Guidelines for Strengthening the Reporting of Menopause and Aging (STROMA) studies. *Maturitas* 2011;70:99–109.
62. Higginson IJ, Evans CJ, Grande G et al. Evaluating complex interventions in end of life care: the MORECare statement on good practice generated by a synthesis of transparent expert consultations and systematic reviews. *BMC Med* 2013;11:111.
63. Gershman MD, Staples JE, Bentsi-Enchill AD et al. Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunisation safety data. *Vaccine* 2012;30:5038–58.
64. Sargeant JM, O'Connor AM, Dohoo IR et al. Methods and processes of developing the strengthening the reporting of observational studies in epidemiology – veterinary (STROBE-Vet) statement. *Prev Vet Med* 2016;134:188–96.
65. Cheng A, Kessler D, Mackinnon R et al. Reporting Guidelines for Health Care Simulation Research: Extensions to the CONSORT and STROBE Statements. *Simul Healthc* 2016;11:238–48.
66. White RG, Hakim AJ, Salganik MJ et al. Strengthening the Reporting of Observational Studies in Epidemiology for respondent-driven sampling studies: “STROBE-RDS” statement. *J Clin Epidemiol* 2015;68:1463–71.
67. Schriger DL. Suggestions for improving the reporting of clinical research: the role of narrative. *Ann Emerg Med* 2005;45:437–43.
68. Hrynaskiewicz I, Norton ML, Vickers AJ, Altman DG. Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers. *BMJ* 2010;340:c181.
69. Olson SH, Voigt LF, Begg CB, Weiss NS. Reporting participation in case-control studies. *Epidemiology* 2002;13:123–6.
70. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010;19:537–54.

Registration and ethics committee approval for observational studies:

Current status and way forward



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Abstract

Randomised controlled trials (RCTs) have always been recognised as the highest level of evidence in medical research. However, they cannot address the questions that one comes across in real-world clinical practice. Observational studies can answer such questions as they are based upon real data obtained from patient healthcare records, medical databases, and registries. Literature review has shown that observational studies are as important as RCTs and should be considered when making any clinical decisions. However, there is a lack of standard guidelines for registering and reporting observational studies, which may contribute to publication and reporting bias. Furthermore, guidelines differ on the ethical considerations for observational studies. This article discusses these issues, focusing on the current situation and gaps in the registration, ethics approval, and publication of observational studies.

Background

Randomised controlled trials (RCTs) investigate the efficacy of new interventions and are considered the gold standard in medical research. They are considered strong evidence in the hierarchy of evidence-based medicine (EBM) because of their well-defined study designs, compliance with strict protocols, and trans-

parency (Figure 1). However, RCTs are performed under tightly controlled conditions and, thus, their results are limited to the patients in experimental settings. Real-world clinical practice comes up with many different situations that might not have been tested in a clinical trial. There can be a new adverse event, an off-label indication, a co-morbid condition, or a co-

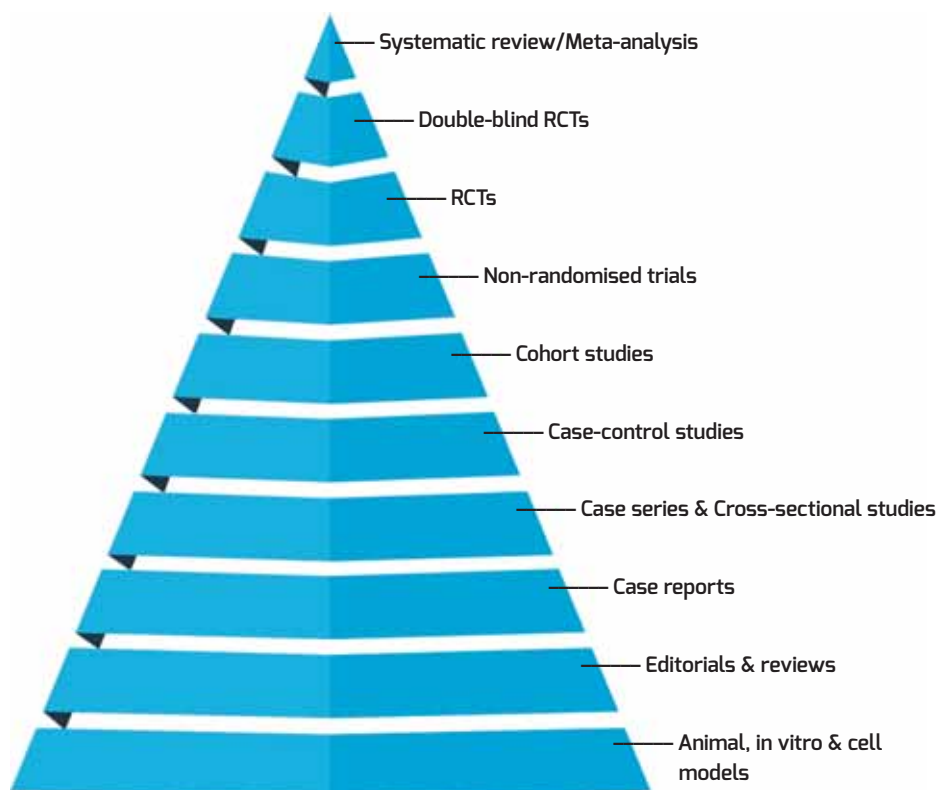


Figure 1. Level of evidence in medical research.⁴ The positions of randomised controlled trials and observational studies in the pyramid of evidence for medical research are shown.

medication that can change the course of the illness. In such situations, an observational study can provide answers to many questions and can supplement the clinical trial in applying the intervention to the general population.^{1–4}

In observational studies, the interventions are not determined by the protocol and are based on real-world clinical practices. These studies are based upon data obtained from patient health-care records, health care databases, and registries, and can be prospective or retrospective in nature. Observational studies can be of various types, including cross-sectional, case-control, and cohort studies; however, their main strength lies in the fact that they are more proximate to real-life evidence.^{1–3}

Going beyond randomised controlled trials: Where do observational studies stand?

Benson et al compared observational studies with RCTs across 19 diverse treatments and found summary estimates of the treatment effects to be similar for both types of studies.⁵ Further, Concato et al identified meta-analyses of RCTs and observational studies for five clinical topics and found the summary estimates and 95% confidence intervals (CIs) to be similar. For example, the odds ratio (95% CI) was found to be 0.49 (0.34–0.70) and 0.50 (0.39–0.65), respectively, for RCTs and observational studies assessing the effectiveness of the Bacillus Calmette-Guérin vaccine against active tuberculosis.⁶ Furthermore, literature shows that observational studies are being used by the American Geriatrics Society, the Endocrine Society, and various other vitamin D expert groups to make recommendations on vitamin D supplementation.⁷

RCTs and observational studies need to be viewed together because their different study designs and methods are crucial to provide as much information as possible in terms of the safety, efficacy, and effectiveness of an intervention.^{8,9} RCTs might not give accurate answers in complex situations, for example the presence of confounding factors, interventions of long duration, larger patient populations, and use of concomitant medications. Observational studies can, and should, be used in such complex domains to explore the best practices in the real world; however, their findings should be considered with due caution.^{2,4}

There are instances where FDA decisions

have been based on observational study results, such as the Data Collection on Adverse Events of AntiHIV Drugs (D:A:D) study. The D:A:D study was conducted in 33,347 HIV-1-infected patients and showed that the risk of heart attack increased by 49% and 90%, respectively, with the use of didanosine and abacavir. On the basis of these study results, the FDA advised healthcare providers to evaluate the risks and benefits of HIV antiretroviral drugs, including abacavir and didanosine.¹⁰

Ensuring the quality of observational studies: What do the guidelines say?

To ensure the quality of observational studies,

various guidelines have been published by scientific and regulatory organisations. The guidelines identified in the literature along with their key objectives are summarised in Table 1.^{11–20}

Literature review shows that these guidelines are not all in agreement on standards of observational studies: There was no consensus for 12 out of the 23 elements discussed in the guidelines. This may contribute substantially to disparities in research and, thus, a low quality of evidence for patient care decisions, leading to poor healthcare outcomes. Moreover, there is a lack of standards for ethical considerations and dissemination. Only three out of nine guidelines addressed these aspects; however, no actions were suggested regarding implementation.¹¹

Table 1: Guidelines for observational studies

Guideline	Key objective
1 Agency for Healthcare Research Quality (AHRQ): Developing a Protocol for Observational Comparative Effectiveness Research ¹²	To identify the minimum standards and best practices for designing observational comparative effectiveness research studies
2 Comparative Effectiveness Research Collaborative Initiative: Observational Study Assessment Questionnaire ¹³	To assess the relevance and credibility of observational studies for informed health care decision making
3 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols ¹⁴	To consider the important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol
4 ENCePP Guide on Methodological Standards in Pharmacoepidemiology ¹⁵	To provide methodological guidance for researchers in pharmacoepidemiology and pharmacovigilance
5 United States Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment ¹⁶	To provide guidance on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs
6 Good ReseArch for Comparative Effectiveness (GRACE) Checklist ¹⁷	To provide a checklist for observational comparative effectiveness studies that are rigorous in design to help in decision support
7 GRACE Principles ¹⁸	To help decision makers evaluate the quality of observational research studies of comparative effectiveness
8 International Society for Pharmaco-economics and Outcomes Research (ISPOR) Good Research Practices for Retrospective Database Analysis Task Force Report ¹⁹	To provide guidance on framing research questions and reporting findings for retrospective epidemiologic and health services research studies
9 Patient-Centered Outcomes Research Institute (PCORI) Methodology Standards ²⁰	To provide guidance on various topics, including formulating research questions, data integrity and analysis, data registries, and systematic reviews

Ethical principles for medical research

As per the Declaration of Helsinki, medical research involves research on identifiable human material or data and needs to be continuously challenged to prove the efficacy, effectiveness, or quality of prophylactic, diagnostic, and therapeutic procedures. The design and results of all clinical studies should be publicly available and are subject to ethical standards. Furthermore, all experimental procedures involving human beings should be well-defined in a protocol, which needs to be approved by an ethics committee.²¹

The two most important points to be considered are registration of clinical studies and ethics committee approval of any study involving human beings. In this article, we discuss the current status of these two points in reference to observational studies, as well as future implications.

Registration of observational studies: Current situation and gaps

Registering clinical trials is not only ethical but also has a scientific rationale. It provides global access to information, reduces duplication, enables monitoring for adherence to ethical principles and regulations, improves the credibility of the information, accelerates knowledge creation, and ensures transparency of research.²²

As per Food and Drug Administration Amendments Act (FDAAA) 801 requirements, there is no mandatory requirement for observational studies to be registered on ClinicalTrials.gov, unlike RCTs.²³ Thus, observational studies are quite vulnerable to publication and reporting bias, owing to selective reporting, misinterpretation of analyses, and lack of regulations related to their registration and reporting. This undermines the overall validity of observational studies and provides a rationale for registering them.^{22,24}

Currently, ClinicalTrials.gov allows the registration of observational studies and provides specific data elements to be filled in for registration. In Europe, the European Union electronic Register of Post-Authorisation Studies (EU PAS Register) is publicly available for registration of post-authorisation studies to improve the transparency of observational research.^{25,26}

Over the past few years, the number of observational studies registered per year has

increased and observational studies now represent about 15% of all studies on ClinicalTrials.gov. Around half of these studies are from North America (50%), followed by Europe (20%) and Asia (13%), and 85% are funded by non-industry sources. However, the number of observational studies registered is still considered low, exposing observational studies to reporting bias.^{24,27}

Some of the challenges in the registration of observational studies include:²⁴

- Most of the studies registered are prospective in nature, and there is a need to establish methods for registering other types of studies, such as retrospective studies
- The timeframe for registering observational studies needs to be defined, along with the attributes that should be mentioned
- Whether or how to register sub-studies or secondary studies using the same prospective data
- Defining the data elements for reporting different types of observational studies

To ensure complete transparency of observational studies, these issues need to be properly addressed. This requires discussions among all stakeholders, including sponsors, regulatory authorities, and the public.²⁴

Ethics committee approval of observational studies: Current situation and gaps

Although it is clear from the Declaration of Helsinki that research protocols must be approved by an ethics committee before the start of any experimental procedure, the situation is a little confusing for observational studies. Some countries may waive the requirement for ethics committee approval of observational studies because there is no experimental intervention.²⁸ Currently, ethics committee approval is needed for all research in Canada, including the review of

patient records.²⁹ By contrast, retrospective studies are excluded from the code of ethics approval in Turkey.³⁰

Ethics committee approval of observational studies has been a topic of great debate. This is well illustrated by the differences in opinion in the literature. While Orchard (2008) argued that most observational studies are not ethically sensitive and that ethics requirements are an unnecessary barrier, others (Moser and Röggla, 2008) disagreed, stating that ethical requirements are important to prevent bad practices in research.^{31,32}

Observational studies and publications

Differences in guidelines on observational studies may lead to serious confusion when it is time to publish them. This is illustrated by a case in which manuscripts based on various French observational studies were rejected or retracted by US peer-reviewed journals because the protocols had not been approved by an ethics committee. As per French law, which comes under the European regulations, only biomedical research involving an intervention and not performed in the normal medical follow-up of patients needs ethics approval. The authors of the French studies stated that ethics approval was not sought as the studies were performed using routine techniques. However, this was against US requirements and, thus, the studies were rejected. One important point to consider here is that even if there is no requirement for ethics approval of such studies in France, it is compulsory to have an ethics opinion.³³

In 2004, an international initiative, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), was launched to provide guidance on the reporting of observational studies. The STROBE guidelines include a complete checklist of items that need to be addressed when reporting observational studies (e.g. study design, participants, and results), but there is no mention of ethical requirements and regis-



Table 2: Statements to be included in manuscripts based on observational studies, as per the ICMJE recommendations and journals' author instructions³⁵⁻⁴⁰

Organisation/ Journal	Statement
ICMJE	"The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included."
BMJ	"Every research article submitted should include a statement that the study obtained ethics approval (or a statement that it was not required), including the name of the ethics committee(s) or institutional review board(s), and the number/ID of the approval(s)."
JAMA	"For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Methods section. For those investigators who do not have formal ethics review committees, the principles outlined in the Declaration of Helsinki should be followed."
PLOS ONE	"Methods sections for submissions reporting on any type of observational and field study must include ethics statements that specify: permits and approvals obtained for the work, including the full name of the authority that approved the study; if none were required, authors should explain why."
Lancet	"Studies on patients or volunteers need approval from an ethics committee and informed consent from participants. These should be documented in your paper."
Springer	"The following statements should be included in the text before the References section: Ethical approval "Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards." For retrospective studies "Ethical approval: For this type of study formal consent is not required."

Abbreviations: BMJ, British Medical Journal; ICMJE, International Committee of Medical Journal Editors; JAMA, Journal of the American Medical Association

tration.³⁴ However, the International Committee of Medical Journal Editors (ICMJE) along with specific international journals clearly mention the ethical requirements and considerations when submitting observational studies for publication (Table 2).³⁵⁻⁴⁰

Ultimately, the Committee on Publication Ethics recommend ethics approval for all observational studies or suggests that a supporting letter be requested from the ethics committee in cases of exemption (where ethics approval is not required).^{41,42} It should be understood that regulatory authorities and legal bodies are not enemies of research but are working towards improving research practices to the ultimate benefit of patients and society.²⁸

Key messages

- Observational studies are as important as RCTs and play an important role in real-world evidence.
- Currently, there are no standard guidelines on registration and ethics committee approval of observational studies.
- It is not mandatory to register observational studies and obtain ethics committee approval before study start.
- There are no standards on dissemination of data from observational studies, and this creates confusion in the publication process.
- Creating standardised guidelines for all these aspects would help to improve the transparency of research and validate the findings

of observational studies. This would help to avoid the duplication of data and misinterpretation of results, and would contribute to the worldwide spread of knowledge.

- It is advantageous for researchers/sponsors to register their studies and consider ethical requirements because the ultimate aim is to improve patient healthcare and thereby benefit society.
- The ideal process for conducting and publishing an observational study is illustrated in Figure 2.

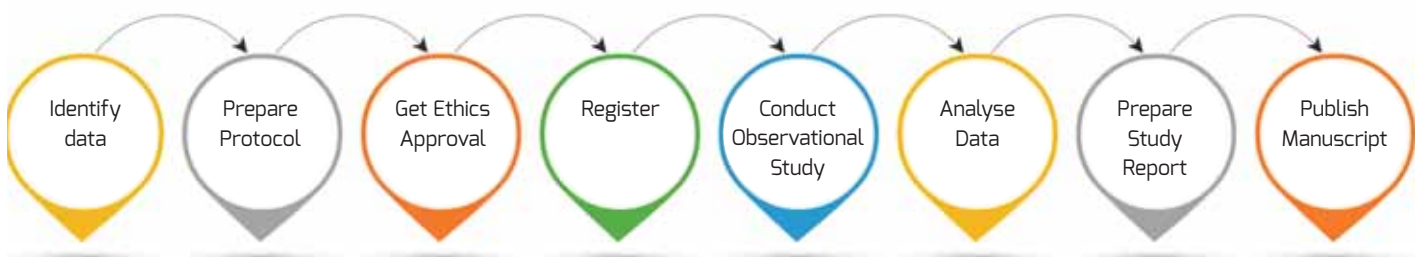


Figure 2. The ideal process for designing, conducting, and publishing an observational study.

References

1. Song JW, Chung KC. Observational studies: cohort and case-control studies. *Plast Reconstr Surg* 2010;126:2234-42.
2. Silverman SL. From randomized controlled trials to observational studies. *Am J Med* 2009;122:114-20.
3. Mariani AW, Pêgo-Fernandes PM. Observational studies: why are they so important? *Sao Paulo Med J* 2014;132:1-2.
4. Schillaci G, Battista F, Pucci G. Are observational studies more informative than randomized controlled trials in hypertension? Con side of the argument. *Hypertension* 2013;62:470-6.
5. Benson K, Hartz AJ. A comparison of observational studies and randomised, controlled trials. *N Engl J Med* 2000;342:1878-86.
6. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;342:1887-92.
7. Grant WB. Using findings from observational studies to guide vitamin D randomized controlled trials. *J Intern Med* 2015;277:83-6.
8. Faraoni D, Schaefer ST. Randomized controlled trials vs. observational studies: why not just live together? *BMC Anesthesiol* 2016;16:102.
9. Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. *JACC Cardiovasc Interv* 2008;1:211-7.
10. FDA. Early Communication about an Ongoing Safety Review of Ziagen (Abacavir) and Videx (Didanosine). 2017 [cited 2017 June 07]. Available from: <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm070263>.
11. Morton SC, Costlow MR, Graff JS, Dubois RW. Standards and guidelines for observational studies: quality is in the eye of the beholder. *J Clin Epidemiol* 2016;71:3-10.
12. AHRQ Methods for Effective Health Care. Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM, editors. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 [cited 2017 June 07]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23469377>.
13. Berger ML, Martin BC, Husereau D et al. A questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: an ISPOR-AMCP-NPC good practice task force report. *Value Health* 2014;17:143-56.
14. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP Checklist for study protocols (revision 3). 2017 [cited 2017 June 07]. Available from: http://www.encepp.eu/encepp/openAttachment/methodologicalDeclaration/19034;jsessionid=8FX83-nDtJBQU68dzHjDZj-TG4Z_eH1Qto6W0iqP5tEamNws3gbL!298584184.
15. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (revision 5). 2017 [cited 2017 June 07]. Available from: http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_Rev5.pdf.
16. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry: good pharmacovigilance practices and pharmacoepidemiologic assessment. 2007 [cited 2017 June 07]. Available from: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf>.
17. Dreyer NA, Velentgas P, Westrich K, Dubois R. The GRACE checklist for rating the quality of observational studies of comparative effectiveness: a tale of hope and caution. *J Manag Care Spec Pharm* 2014;20:301-8.
18. The GRACE Initiative. GRACE principles: Good ReseArch for Comparative Effectiveness. 2017 [cited 2017 June 07]. Available from: <https://www.pharmacoepi.org/pub/1c29f69f-2354-d714-5100-1ef2b0e9abd9>.
19. Berger ML, Mamdani M, Atkins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomised studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report – Part I. *Value Health* 2009;12:1044-52.
20. Patient-Centered Outcomes Research Institute (PCORI). PCORI Methodology Standards. 2017 [cited 2017 June 07]. Available from: <http://www.pcori.org/research-results/about-our-research/research-methodology/pcori-methodology-standards>.
21. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191-4.
22. Loder E, Groves T, MacAuley D. Registration of observational studies. *BMJ* 2010;340(2):c950.
23. ClinicalTrials.gov. FDAAA 801 Requirements. 2017 [cited 2017 June 07]. Available from: <https://clinicaltrials.gov/ct2/manage-recs/fdaaa>.
24. Williams RJ, Tse T, Harlan WR, Zarin DA. Registration of observational studies: is it time? *CMAJ* 2010;182:1638-42.
25. ClinicalTrials.gov. ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies. 2017 [cited 2017 June 07]. Available from: <https://prsinfo.clinicaltrials.gov/definitions.html>.
26. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The European Union electronic Register of Post-Authorisation Studies (EU PAS Register). 2017 [cited 2017 June 07]. Available from: http://www.encepp.eu/encepp_studies/indexRegister.shtml.

27. Boccia S, Rothman KJ, Panic N et al. Registration practices for observational studies on ClinicalTrials.gov indicated low adherence. *J Clin Epidemiol* 2016;70: 176-82.
28. Rasmussen LS, Gisvold SE, Wisborg T. Ethics Committee approval for observational studies. *Acta Anaesthesiol Scand* 2014;58:1047-8.
29. Perlman M. Ethical issues in 'observational research'. *Paediatr Child Health* 2000;5:89-90.
30. Kırac FS. Is Ethics Approval Necessary for all Trials? A Clear But Not Certain Process. *Mol Imaging Radionucl Ther*. 2013;22(3):73-5.
31. Orchard J. For debate: should observational clinical studies require ethics committee approval? *J Sci Med Sport* 2008;11:239-42.
32. Moser B, Röggl G. Should observational clinical studies require ethics committee approval? *J Sci Med Sport* 2008;11:518.
33. Claudot F, Alla F, Fresson J, Calvez T, Coudane H, Bonaïti-Pellié C. Ethics and observational studies in medical research: various rules in a common framework. *Int J Epidemiol* 2009;38:1104-8.
34. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573-7.
35. International Committee of Medical Journal Editors (ICMJE). Preparing for Submission. 2016 [cited 2017 June 07]. Available from: <http://www.icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html#d>.
36. The BMJ. Ethics approval of research. 2017 [cited 2017 June 07]. Available from: <http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/ethics-approval-research>.
37. The JAMA Network. Instructions for Authors. 2017 [cited 2017 June 07]. Available from: <http://jamanetwork.com/journals/jama/pages/instructions-for-authors>.
38. PLOS ONE. Submission Guidelines. 2017 [cited 2017 June 07]. Available from: <http://journals.plos.org/plosone/s/submission-guidelines#loc-observational-and-field-studies>.
39. The Lancet. Instructions for Authors. 2017 [cited 2017 June 07]. Available from: <http://www.thelancet.com/pb/assets/raw/Lancet/authors/lancet-information-for-authors.pdf>.
40. Springer. Publishing ethics. 2017 [cited 2017 June 07]. Available from: <https://www.springer.com/gp/authors-editors/journal-author/journal-author-helpdesk/publishing-ethics/14214>.
41. Committee on Publication Ethics (COPE). Ethics committee approval. 2015 [cited 2017 June 07]. Available from: <https://publicationethics.org/case/ethics-committee-approval>.
42. Committee on Publication Ethics (COPE). Seeking retrospective ethics approval. 2011 [cited 2017 June 07]. Available from: <https://publicationethics.org/case/seeking-retrospective-ethics-approval>.



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Conflicts of Interest and Disclaimers

The authors disclose no conflict of interest.

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Regulatory submissions of non-interventional post-authorisation safety studies:

Challenges for data interpretation and comparisons with clinical data

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Abstract

The post-authorisation safety study (PASS) is a pharmacovigilance activity often required as a post-marketing commitment to establish a safety profile or address specific safety concerns. An imposed PASS must be submitted in common technical document format. Comparability of observational studies to clinical trials is limited by a number of factors related to the differences in design and conduct of these studies. These include selection bias, which is harder to control in the observational setting, and typically a relatively higher extent and quality of data collection in the clinical setting. The PASS also places a strong focus on risk without collecting new formal benefit information. These factors present medical writers with some new (and not so new) challenges.

Offsetting the challenges, the PASS creates opportunities to assess the “real world” prescribing of a drug, to compare the real target population with the label population, and, because of the large scale of such trials, to assess safety across multiple subgroups with greater certainty than possible in a clinical trial.

Introduction

The non-interventional, post-authorisation safety study (NI-PASS) is an increasingly common pharmacovigilance measure, carried out after a medicine has been authorised, to obtain further information on a medicine’s safety. That information may constitute detection of a new, or quantification of an existing safety hazard, or confirmation of a known safety profile.¹

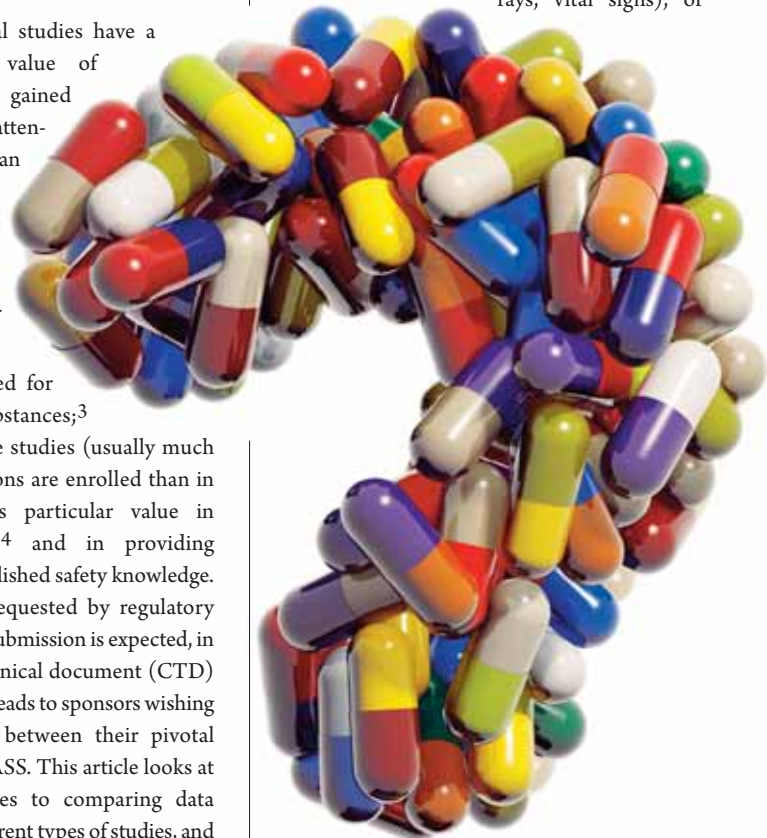
While observational studies have a long pedigree, the value of conducting PASS has gained increasing regulatory attention, and the European Medicines Agency has published a template (similar to that for clinical trials) to aid harmonisation of reporting of PASS.²

A PASS is requested for about half of new substances;³ given the scale of these studies (usually much larger patient populations are enrolled than in clinical trials), it has particular value in identifying rare AEs⁴ and in providing reassurance about established safety knowledge.

When a PASS is requested by regulatory authorities, regulatory submission is expected, in the usual common technical document (CTD) format. This inevitably leads to sponsors wishing to draw comparisons between their pivotal clinical trials and the PASS. This article looks at some of the challenges to comparing data between these very different types of studies, and how the (usually limited), high external validity observational data can complement the (usually thorough), lower external validity clinical data.

Data availability and safety endpoints

The observational setting is limited compared to a clinical trial in terms of the data that can be generated. The principal limitations relate to the fact that interventions other than those that would occur during routine treatment or clinical practice are not permitted in the observational setting. This includes any kind of testing (labs, X-rays, vital signs), or



In terms of terminology, effectiveness is preferred over efficacy for results of observational studies.

even more intensive questioning or study visits other than those that would be part of routine care. Where the product label suggests additional monitoring, data can and should be collected as indicated. Treatment is solely at the discretion of the investigator, and the freedom of dosing, duration of treatment, stopping and starting, changes of dose, and even changes of treatment can confound interpretation of results within the PASS, while providing useful “real-world” information.

While data extraction from medical charts is permissible, monitoring is likely to be less intensive than in a clinical trial, making clarification of missing data challenging. The duration of many trials may also make it difficult or impossible to clarify data at a distance in time. Even basic data such as patient age, sex, and disease history, let alone more critical information such as adverse events (AEs) or causes of death, are far more likely to be absent than in a clinical trial.

The extent of missing data must be considered when making any comparison with prior clinical trials, and the number of missing data points should be quantified wherever possible. Imputation methods must be described in detail, along with any sensitivity analyses. For most soft endpoints (such as biomarkers or quality of life measurements), or those at high risk of reporting bias (such as patient-reported outcomes, including AEs), comparability between a PASS and a clinical trial is often limited, while harder endpoints (such as survival) may be more reliable.

Endpoints requiring measurements or patient questioning are likely to take place less frequently in the observational real world setting than in clinical trials, limiting the value of comparisons. Additionally, the extent and reliability of data collection is usually lower in the PASS. For example, if adverse events are recorded systematically, typical differences to the clinical trial include a longer interval between patient contacts, longer duration of the study (increasing reporting fatigue, higher risk of loss to follow-up), and a focus on particular or established, rather than unexpected, safety issues. Details such as start and stop dates, severity, or countermeasures



are more likely to be vague or missing entirely than in a closely monitored clinical trial. These factors conspire to reduce data availability and limit the comparability of data between the observational and clinical trial settings.

If an overt comparison of AE rates between observational and clinical data is included in 2.7.4, remember that regulators are well aware of these systematic effects. A lower AE incidence rate in the PASS than the clinical trial may not be very informative, but a notably higher AE incidence will probably need explaining; this would of course also apply should a higher AE rate for the primary endpoint (if single event or class of event) is observed in the PASS than in clinical data.

For larger PASS, subgroup data may take more prominence than in typical pivotal-trial based submissions. Studies are almost never powered for subgroups, and formal conclusions cannot be drawn, but the number of patients can provide particularly strong reassurance, or evidence for higher adverse event rates in particular groups.

Demographics

Especially where the screening failure rate is low, the selection of patients and treatments by investigators, which would render a clinical trial

useless, is one of the most important pieces of real-world data to emerge from a PASS. Demographics and background characteristics thus take on a much more important role in the PASS submission than the typical clinical submission, which can often be summed-up as “treatment groups were well-balanced”.

This still needs cautious interpretation, as selection bias can change with increasing experience of a product, whether because the product becomes established or more (or less) affordable or because new safety information causes investigators to restrict use. Furthermore, clinical investigators tend to be more experienced and up-to-date than the medical community in general. The type of patients selected and the quality of treatment at a centre of excellence may well be closer to the “real world” than in a clinical trial but still not be representative of the real world.

The real world usually differs from the clinical trial population in a number of ways. Inclusion and exclusion criteria for clinical trials have a tendency to select patients who are exemplary for the target indication but lack severe comorbidities.⁵ Where the target indication is quantified or graded, the range of severity is likely to be higher, including both sicker and less sick patients, in the PASS than the clinical trials. In terms of comorbidities, again, the selection for clinical trials tends to reduce the proportion of patients with other diseases, while the PASS should have no such restrictions beyond those in the label. This results in a wide variety of confounding factors and the need to consider their impact on the main safety results. Differences between groups in multiple-arm PASS should be discussed and sources of bias that may explain the differences mentioned. Extent of comorbidity and disease severity are worthwhile considering for subgroup definitions, at the latest during drafting of the statistical analysis plan.

Efficacy or effectiveness

By definition, a PASS is preceded by a Phase III submission, and the Phase III studies typically inform the design of the PASS. Inclusion and exclusion criteria should be minimal and are usually broad enough to capture every patient

who receives the treatment at study sites. In some cases, particularly where there are multiple study arms, some effort will be made to recruit similar subjects across arms (reinforced by the product label), or at least to restrict the study to the particular indication. Some outcomes may be recorded that lend themselves well to comparison with the previous Phase III studies, in particular analysis based on spontaneously reportable events that are at low risk of being missed or falsely recorded.

Hard endpoints, such as death, recurrence of the disease under treatment, or hospitalisations, can often be evaluated on the basis of routine data collection, without prejudicing the observational status of the study. If comparable to efficacy endpoints from the clinical trials, these can be detailed in Module 2.7.3, provided it is made clear that, formally, the results arise from safety analyses in the PASS. Because PASS studies are not conducted to investigate efficacy, no efficacy claims should be made, even for endpoints that lend themselves well to this and show similar effectiveness to the clinical setting. Comparisons of effectiveness to clinical efficacy data are subject to the same caveats as all other endpoints, due to the considerable differences in study conduct.

In terms of terminology, *effectiveness* is preferred over *efficacy* for results of observational studies. When comparing data directly, other potentially useful terminological distinctions could include *study*, and *patient* (for the PASS) versus *trial* and *subject* for the clinical trial. These, however, will not excuse an otherwise inadequate distinction between the data sources. Imposing such subtle differences of course generates additional writing and QC effort.

Selection bias

Many tools used to reduce bias in clinical trials, such as blinding or randomising, are not available in the observational setting. Potential sources of bias need to be considered very carefully, and discussed in detail, in any submission of data derived from a PASS.

The PASS is particularly prone to selection bias and especially to bias in the allocation of patients to treatment groups within the study. One non-interventional study of an anti-coagulant,⁶ showed a clear but unexpected

difference in all-cause mortality between treatment groups, in favour of the investigational treatment. However, there were important differences between the treatment groups, with patients receiving the investigational treatment less likely to have cancer at baseline, and being younger on average than comparator patients receiving standard treatment.

Prescribing practices for a new medicine change over time, particularly in the first years when experience and knowledge are being gained, and later studies may show different biases than early studies. Even when established imbalances can be traced to particular reasons for clinical decision making, these should be considered anew with each new study.

Selection bias also applies at the point where investigators are considering whether to include patients in the PASS. This can be mitigated by asking investigators to consider for inclusion all (consecutive) patients who are being considered for any of the treatments permitted by the observational plan, reducing the risk that investigator concerns about compliance, likely response to treatment, etc., influence the outcome.

Conclusions

In contrast to most submissions of clinical data the focus for a PASS is on risks, not benefits. Nevertheless, the PASS creates opportunities for interpretation of data beyond the study focus on one or two safety endpoints, in particular in terms of likely real-world usage of the product, how the treated study population differs from that defined in prior clinical trials, and how the safety profile compares across a range of subgroups.

The biases inherent in the design of a PASS differ considerably from those encountered in clinical trials, raising challenges for direct comparisons between the study types, particularly when the PASS has more than one treatment group, where selection bias may confound comparisons even within the PASS treatment groups. Data quality issues may also complicate interpretation, and direct comparisons to clinical data should be made very cautiously. Nevertheless, submission of a PASS offers an opportunity to create a robust safety profile for real-world use of a drug at a relatively early stage in the product lifecycle.

In contrast to most submissions of clinical data, the focus for a PASS is on risks, not benefits.

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References

1. European Medicines Agency. Post-authorisation safety studies (PASS). http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000377.jsp&mid=WC0b01ac058066e979.
2. Morley G. Non-interventional post-authorisation safety studies (NI-PASS): a different type of report. *Med Writ* 2014;23:273-6.
3. Bouvy JC, De Bruin ML, Hoekman J, Stolk P. The costs and effects of post-authorisation safety studies for new active substances. *Value in Health* 2014;17:A445.
4. Cohet C, Rosillon D, Willame C et al. Challenges in conducting post-authorisation safety studies (PASS): a vaccine manufacturer's view. *Vaccine* 2017; 35:3041-9.
5. Kardos P, Worsley S, Singh D, Román-Rodríguez M, Newby DE, Müllerová H. Randomized controlled trials and real-world observational studies in evaluating cardiovascular safety of inhaled bronchodilator therapy in COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:2885-95.
6. Ageno W, Mantovani LG, Haas S et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Haematol* 2016;3:12-21.

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Reporting non-interventional post-authorisation safety studies (NI-PASS)

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Abstract

Post-authorisation safety studies (PASS), whether interventional or, more commonly, non-interventional (NI), can be used by entities such as the European Medicine Agency's Pharmacovigilance and Risk Assessment Committee to oblige drug companies to collect data on approved products. NI PASS study reports should be drafted according to a particular mandated format, which may not be intuitive for writers more familiar with clinical study reports for interventional trials. This article addresses the structure of NI-PASS reports, comparing and contrasting with the clinical study reports of interventional trials.

This article is an update of "Non-interventional Post-Authorisation Safety Studies (NI-PASS): A different type of report," first published in Medical Writing, Volume 23, 2014 – Issue 4.

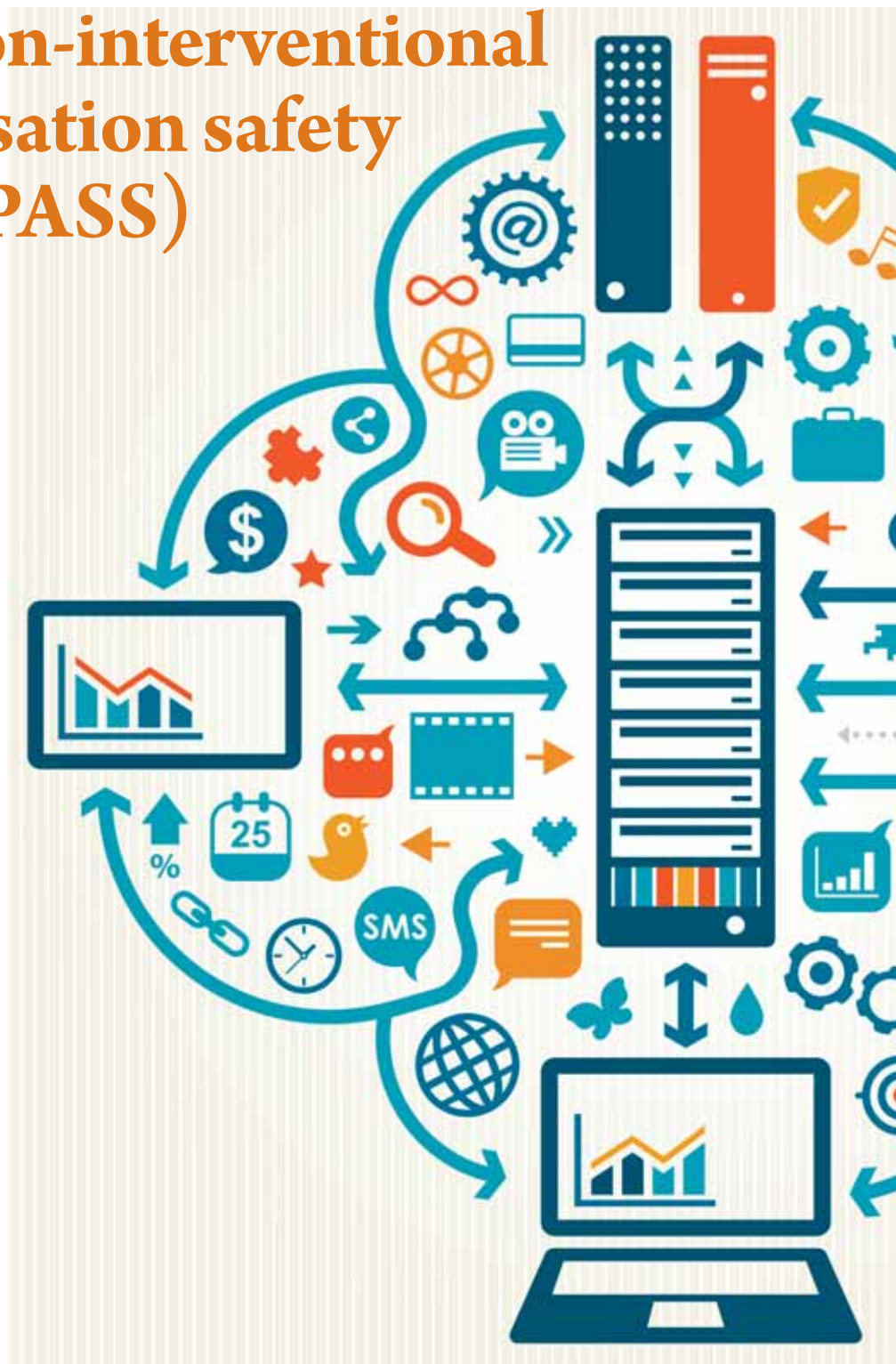
Background

Randomised clinical trials are considered to sit atop the hierarchy of clinical evidence and form the basis for most drug approvals. In contrast, non-interventional studies and observational studies are considered a weaker form of evidence and have, until recently, received little attention from regulatory agencies. There is a growing recognition, however, that randomised clinical trials may not adequately reflect clinical practice; for example, multiple concurrent medications

and illnesses may affect benefit-risk. Furthermore, the number of patients exposed to a drug or the duration of exposure in a clinical development programme may not be sufficient to detect a rare but important safety signal. The Pharmacovigilance and Risk Assessment Committee (PRAC) was set up within the European Medicines Agency in response to this greater emphasis on pharmacovigilance and real-world

data. Specifically, the PRAC's mandate covers:

All aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies (PASS)





and pharmacovigilance audit. (REGULATION [EU] No 1235/ 2010 OF THE EUROPEAN PARLIAMENT)

PASS are therefore an important tool at the disposal of the PRAC for assessing how a medicine behaves outside the confines of clinical trials.¹ According to Directive 2001/83/EC (DIR) Art 1(15),² a PASS is defined as “any

study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.” In particular, these studies are conducted to quantify potential or identified risks, fill gaps in existing safety data, further define risks (or absence thereof), for example after long-term use, or assess the effectiveness of a risk minimisation activity. As such, they may form part of a Risk Management Plan (RMP).

Although a PASS can in principle be an interventional study (which is conducted and reported in accordance with familiar International Conference on Harmonisation [ICH] guidance), the majority are non-interventional studies. In such studies, treatment is assigned according to clinical practice and administered according to approved labeling. Non-interventional PASS studies can include, for example, literature reviews or retrospective analyses of registry data, but non-interventional observational studies are the most common. Like an interventional study, an NI-PASS is also conducted largely in the general spirit of ICH and Good Clinical Practice, but certain aspects may differ. For example, the final study report for an NI-PASS, if submission to the PRAC is required, should be based on the guidance issued by the European Medicines Agency³ and will differ in many features from a typical clinical study report (CSR) for interventional trials (hereafter referred to as “ICH-based CSRs”). The following sections discuss various aspects of NI-PASS reports, with reference where appropriate to familiar ICH-based CSRs.

EU PAS Register

Methodological details of all PASS should be posted to the EU PAS Register, which is run by the European Network of Centres for Pharmacoeconomics and Pharmacovigilance (ENCePP, see <http://www.encepp.eu/>). Much has been made about the need to disclose interventional trial protocols and results in the interests of transparency, and this is the analogous requirement for NI-PASS. The study results, once available, should be posted to the website within 2 weeks of submission of the final study report (in turn usually submitted within 1 year of completion of data collection).³ Some companies post the entire report (with redactions and

stripped of the appendices) while others opt for posting the report abstract.

Most pharmaceutical companies now scrupulously post details of interventional trials on sites such as clinicaltrials.gov, but observational studies – particularly the older ones – may have been overlooked. It is worth checking early on in the drafting procedure whether the study has been registered on the ENCePP website and assigned an EU PAS registration number necessary for completion of the final study report.

Structure of NI-PASS reports

A guidance document covering the format and content of the final study report of NI-PASS was issued in 2013.⁴ The guidance document suggests that the table of contents of the guidance document itself can be used to build a template for the NI-PASS report (see Figure 1). As noted above, the type of PASS can vary widely, and a single template might not always cover the reporting needs. Often there will be section headings without any content. In these cases, a sensible approach would be to keep the headings of the structure given in the guidance with “not applicable” if appropriate. Extra headings and subheadings can be added if necessary. By analogy with ICH-based CSRs, guidance-mandated sections do not have to be considered as separate numbered sections in the report. Thus, the abstract does not necessarily need to be numbered as Section 1.

Cover page

The format of the cover page is mandated by the guidance and should be fairly self-explanatory. As described above, the EU PAS Register number is required information.

Abstract

Unlike the synopsis of an ICH-based CSR, an NI-PASS report has a structured abstract, in some ways similar to a journal abstract but with more subheadings. The structure of the abstract is defined by the guidance and, in addition to the title and key words, includes rationale and background, research question and objectives, study design, setting, subjects and study size, variables and data sources, results, and discussion. The guidance actually states that the word count (excluding the title and certain other administrative details) should not exceed 500 words. With so many subheadings, and for a

1.	Abstract	10.	Results
2.	List of abbreviations		10.1. Participants
3.	Investigators		10.2. Descriptive data
4.	Other responsible parties		10.3. Outcome data
5.	Milestones		10.4. Main results
6.	Rationale and background		10.5. Other analyses
7.	Research question and objectives		10.6. Adverse events/adverse reactions
8.	Amendments and updates	11.	Discussion
9.	Research methods		11.1. Key results
	9.1. Study design		11.2. Limitations
	9.2. Setting		11.3. Interpretation
	9.3. Subjects		11.4. Generalisability
	9.4. Variables		
	9.5. Data sources and measurement		
	9.6. Bias		
	9.7. Study size		
	9.8. Data transformation		
	9.9. Statistical methods		
	9.9.1. Main summary measures		
	9.9.2. Main statistical methods		
	9.9.3. Missing values		
	9.9.4. Sensitivity analyses		
	9.9.5. Amendments to the statistical analysis plan		
	9.10. Quality control		

Figure 1. Suggested structure of NI-PASS according to the EMA guidance (4).

study of any complexity, this will be challenging. As far as I am aware, this word count can be exceeded (in the same way that the synopsis of an ICH-based synopsis may if needed exceed 3 pages). Sensible advice here would be to keep as close to 500 words as possible without omitting any important features, results, or conclusions of the study, particularly if the abstract rather than the entire report is to be used when disclosing results.

Administrative sections and methodology

As with an ICH-based CSR, the first part of an NI-PASS report has sections covering administrative aspects (investigators, other responsible parties, milestones) and research methods. In the case of protocols written according to the latest NI-PASS guidance,⁵ the methodology sections can be adapted from the corresponding sections in the protocol. The correspondence is not exact; report subsections such as “Bias”, “Subjects”, and “Sensitivity analyses” do not have an exact counterpart in the protocol, although issues such as bias and the need for sensitivity analyses may be addressed in protocol sections such as “Data analysis” and “Limitations of the research

methods”. When writing an NI-PASS protocol, it might be helpful to have the guidance for final study reports in hand as this may facilitate subsequent drafting of the NI-PASS report. If the NI-PASS study was initiated prior to 2012 (when the PRAC became operational), then it is unlikely that the study was conducted with a protocol drafted according to the latest guidance or has been submitted to PRAC. The study protocol may therefore not follow the mandated protocol format and the methods section will require more thought and work to map out content. The writer will have to refer to the guidance text to ensure that the content is appropriate, especially as some section headings are not intuitive for someone used to writing ICH-based CSRs.

For an ICH-based CSR, it is generally considered good practice to extensively cross-reference the protocol. In the case of an NI-PASS report, however, the protocol may not necessarily be appended to the CSR, although details of the methods should of course be available on the register website. To enhance readability, the methods section of an NI-PASS report should perhaps be more stand-alone than

an ICH-based CSR counterpart.

The report structure also includes a section titled “Amendments and updates”, which unlike the equivalent section in an ICH-based CSR, refers only to amendments to the protocol. Changes to the statistical analysis are presented as part of the results.

Results

The structure of the report as presented in the guidance has six sections. The “Participants” section is self-explanatory. The next section “Descriptive data”, according to the guidance text, refers largely to patient characteristics. As NI-PASS are by definition non-randomised studies, it is important to have a good understanding of the baseline characteristics of different patient groups in order to assess potential biases when making group comparisons. The “Outcome data” section should include, according to the single line of guidance text for this section, the “numbers of subjects across categories of main outcomes”. This section is likely intended to reflect that there are often considerable amounts of missing data in observational studies. As there are other sections where outcome results can be included (for example, “Main results” and “Other analyses”) one interpretation is that this subsection could be considered as roughly equivalent of the Section “Analysis populations” in an ICH-based CSR.

The last subsection of the Results section is “Adverse events/adverse reactions”. Detailed guidance is given for this particular subsection, which will likely closely resemble the adverse event-reporting section of an ICH-based CSR. If applicable, a clear, well-structured subsection here will enable ready incorporation of data into other documents such as a Periodic Benefit Risk Evaluation Report.

Discussion

For many ICH-based CSRs, the standard advice is to keep the discussion section brief and fairly non-committal, the argument being that higher-level documents such as the clinical overview are more appropriate places to relate the study findings to the rest of the clinical development programme and the literature. The template for an NI-PASS, however, with four separate subsections (key results, limitations, interpretation, and generalisability), invites an involved discussion.

This part of the final study report will also be

easier to write if the protocol has been written in the NI-PASS template. For example, the “Limitations” subsection can largely be based on the “Limitations of the research methods” in the protocol, enhanced with post-hoc knowledge and understanding gleaned from the results. Most observational studies will be subject to similar limitations (bias, for example) and similar strengths as well (greater applicability to clinical practice, a point that is specifically addressed in the “Generalisability” subsection).

Appendices and annexes

The template has the option of including appendices. These would likely include certain key study documentation such as the protocol and selected summary tables not included in the report body. No details are given as to how to structure this information, so it is probably reasonable to follow the approach used by the company for ICH-based CSRs. Annex 1 (mandatory) is a list of documents available on request (for example, listings) while Annex 2 is for any additional information.

NI-PASS: Past, present, and future

When I first wrote about NI-PASS reports in 2014, these types of report were relatively new, and my advice then was check the EMA website occasionally for updated guidance. For this update, I took my own advice but could not find anything new of significance for actual report drafting (although detailed procedural guidance is now available). However, given that some companies include the full (but appropriately redacted) report on the ENCePP website, an increasing number of examples are becoming available. Unfortunately, the search functionality of the ENCePP website does not allow filtering of results by availability of a final report, so you will need to look one by one. Nevertheless, with patience, it should be possible to retrieve some relevant examples of the approach of other writers and their interpretation of the guidelines.



References

1. Guideline on good pharmacovigilance practices (GVP): Module VIII – Post-authorisation safety studies (Rev 1). 19 April 2013. EMA/813938/2011 Rev 1. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf.
2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal of the European Communities L 311/67. 28.11.2001. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF>.
3. EU PAS Register Guide. European Medicines Agency. 28 July 2014, EMA/613603/2012. Available from <http://www.encepp.eu/publications/documents/EUPASRegisterGuide.pdf>.
4. Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies. 30 July 2013. EMA/48663/2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf.
5. Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies. 26 September 2012. EMA/623947/2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf.

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Patient-reported outcomes: How useful are they?

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Abstract

Patient-reported outcomes (PROs) are any report on the status of a patient's health condition as told by the patient him or herself or through an interview, without any interpretation by a clinician or anyone else. They generate information on those aspects of health, disease, and treatment that are only known to the patient suffering from the condition, and include any assessment of symptoms, functional status, psychological and social well-being, health related quality of life, adherence, persistence, satisfaction, or preferences for healthcare interventions from the perspective of the individual. In clinical research, PROs are endpoints of observational studies and provide data on patients in real life situations. The appropriate selection of PRO and of PRO instruments as well as the accurate interpretation and reporting of PRO results are essential to the reliability of evidence generated. PRO assessment has become a vital component in the design of patient registries, which should serve to improve the provision of healthcare, to inform decision makers, and to gain knowledge on the true effects of treatments on patients in the long term.

Introduction

Patient-reported outcomes (PROs) reflect what patients think and how they feel about their disease and treatment(s) they receive.¹ They

provide information on patients' views, attitudes, and behaviours that ultimately determine the effectiveness of therapies in real life situations and usual clinical practice. PROs are captured and measured by specifically designed and validated instruments and methods to cover many aspects of the individual such as social and psychological well-being, physical and social functioning, health related quality of life (HRQoL), preferences, adherence, persistence, and satisfaction. Because they depict the results of treatments in real life they are most frequently measured in observational studies.² As a result, PROs complement highly valuable data on the efficacy and safety information usually generated in clinical trials. This article gives definitions of PRO, descriptions of tools used, and reporting requirements as well as the fundamentals for arguing that PRO assessment in observational studies are generators of data that are as important as data from clinical trials.

What are patient-reported outcomes?

PRO is defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" by the US Food and Drug Administration (FDA).³ In Europe, the European Medicines Agency (EMA)⁴ adds that PROs are "based on patient's perception of a disease and its treatment(s)" and that PRO is "an umbrella term covering both single dimension and multi-dimension measures of symptoms, HRQoL, health status, adherence to treatment, and satisfaction with treatment".⁴

PROs provide information on those aspects of health, disease, and treatment that are only known to the patient suffering from the condition, such as the frequency, severity, and emotional repercussion of symptoms, the impact of the illness in everyday life, or the factors determining beliefs and behaviours towards treatments.⁵ They allow investigators and clinicians to know about their patients' thoughts and perceptions on the healthcare process and

Table 1. Type of PRO instruments and related information

Type of PRO instrument	Concept measured	Advantages	Disadvantages	Example
Generic	Health status and outcomes of illness	Applicable to the general population and to a wide range of patient groups	Some levels of detail that may be relevant to specific disease groups are sacrificed	36-Item Short Form Survey Instrument (SF-36)
		Assess an extensive variety of aspects of health and disease	Not sensitive to changes in health that may be clinically important	
		Suitable for use across a broad range of health problems		
		Suitable for comparing treatments for different disease groups		
		Useful for assessing the impact of healthcare technologies in which therapeutic effects are still uncertain		
Utility measures	Preferences or values attached to individual health states	Produces information on the overall value of health states to society	Labour-intensive and time-consuming	5-dimension-5 level EuroQol questionnaire (EQ-5D-5L)
		Useful for economic evaluation studies	Respondents may have difficulty understanding the tasks they are required to perform	
Disease specific	Patient's perceptions of a specific disease or health problem	Relevant to patients suffering from the disease	Health status scores cannot be compared with those obtained for the general population	Audit of Diabetes Dependent Quality of Life (ADDQoL)
		Relevant to clinicians as it is responsive to clinically important changes resulting from interventions directed to control the health problem	Comparisons across treatments for different diseases are not possible	
			May not be sensible for detecting side effects or unforeseen effects of treatment	
Population specific	Particular demographic groups' perceptions of disease (e.g. children or elderly people)	Content more relevant to the group in question	Health status scores cannot be compared with those obtained for the general population	Child Health and Illness Profile-Child Edition (CHIP-CE)
		Specifically tailored format (e.g. cartoon illustrations)	Comparisons across population groups may not be possible	
		More sensitive to systematic differences between population groups		
Dimension specific	Severity of symptoms (or other dimension of disease) and their impact on functioning, role activities, psychological and social well-being	Provide a more detailed assessment of a particular dimension of health	Not appropriate as a solely outcomes measure for the evaluation of the effectiveness of treatment	Brief Symptom Inventory (BSI)
Individualised	Issues, concerns, or domains of personal concern to the respondent	High content validity	Have to be administered by interview: labour-intensive and time-consuming	Schedule for the Evaluation of Individual Quality of Life (SEIQoL)

Note: Based on Oxford University Patient Report Outcomes Measurement Group⁶

Table 2. Fundamental properties of a PRO instrument

Properties	Definition
Reliability	Ability to yield the same result on serial administrations when no change in the concept being measured is expected. Individuals with the same health status or fairly the same disease situation will score similarly in the PRO instrument.
Responsiveness	Ability of the instrument to detect changes that occur over time in individuals or group of individuals who have experienced modifications on their health status or disease development (e.g. improvements, deterioration, or an unexpected event) or have received a treatment of demonstrated efficacy. The changes in the PRO instrument scores will vary accordingly in direction and magnitude as the individual's health or disease situation change in time.
Validity	Degree to which the instrument measures what it intends to measure.
Construct validity	Degree to which what was measured reflects the conceptualisation of what should be measured.
Content validity	Extent to which the instrument actually measures the concepts of interest.
Criterion validity	Extent to which the scores of the PRO measured reflect the gold standard measure of the same concept.
Minimal clinically important difference (MID)	The smallest change in score in an instrument that can be regarded as important and meaningful from the patient's or clinician's perspective.

Note: Based on Frost et al.⁹

expected results that tests, technologies, or other observers cannot unveil.⁶ In this sense, accounting for PROs helps to empower patients and enhance communication among patients, healthcare providers, and decision makers. They also help to anticipate the probable effectiveness of therapies.⁷

PRO instruments

PRO instruments are the tools patients use to assess their health conditions, health status, and other physical, social, and mental functions as they perceive these. They are administered by the patient (self-reported), by a health-care provider through interviews, or by a combination of both. Responses are in the form of scoring (e.g. from 1 to 5) or ordering (e.g. highest to lowest), or by choosing amongst a set of answer options (e.g. the most and the least important), which can consist of pictures, numbers, or categories.¹ PRO instruments can be classified based on the concept they measure (Table 1 overleaf).⁶

Ideally, a PRO instrument should be specific to the concept (e.g. health status) being measured within a framework of robust evidence gathered earlier. Moreover, it should contain an optimum number of items to minimise response overload, have scales of easy use (if possible, the simplest for the intended population to understand), be reproducible, and maintain patient confidentiality.⁵

A PRO instrument can be administered on paper or electronically (e-PRO) through

electronic diaries, computers, telephones, and other portable devices.⁶ Compared with paper-based PROs, e-PROs are more beneficial because they

- generally reduce missing information and avoid data entry errors, which usually arise from an intermediate source,
- are immediately accessible,
- trigger alerts and notifications,
- increase patient's willingness to report sensitive information, and
- give real-time tracking of survey compliance.

However, there are some important barriers in their use such as increased expense, some cultural resistance, and limited time for patient-training.⁷

Selection of PRO instruments

Verifying that a proper PRO instrument has been selected is vital to adequately interpret results and consequently enhance the chances of publication. If PRO results are to be used in labelling claims, they should also satisfy regulatory requirements.⁸ Three properties of a PRO instrument are fundamental: validity, reliability, and responsiveness (Table 2).⁹ The calculation of the minimally important difference (MID) is also relevant. Beyond those critical characteristics, a series of additional aspects should also be taken into account to assess the appropriateness of the chosen PRO instrument

For purposes of economic evaluations, a PRO instrument should focus on less complexity, speed, and sensitivity to incremental effects on HRQoL and to choices in decision making.

(Table 3). If preferences for health states or for the characteristics of treatment are considered, the most appropriate method for eliciting patients' preferences should be ensured. Examples of preference assessment include ranking or rating scale, best-worst scaling, standard gamble,

time trade-off, visual analogue scale, discrete choice experiment and conjoint analyses, and multi-attribute utility instruments.^{10,11}

However, other considerations in selecting a PRO instrument are the setting, nature, and aim of the project, and the type of healthcare decision to be made.¹² For example, a PRO instrument for registries of patients' health records should prioritise its practicality, easy administration, cost-effectiveness, low participant burden, and simple documentation with other clinical data. PRO instruments for product labelling should reinforce high validity and reliability, sensitivity to changes, instrument stability over time, and low rates of missing data. For purposes of economic evaluations, a PRO instrument should focus on less complexity, speed, and sensitivity to incremental effects on HRQoL and to choices in decision making.¹³

There are some institutions that provide accurate information on the characteristics and properties of the PRO instrument as well as use and reporting recommendations and bibliographic references. One is the Mapi Institute,

which maintains the Patient-Reported Outcome and Quality of Life Instruments Database,¹⁴ allowing users to search a large and comprehensive database for PRO instruments. Here, the user can find the best PRO that addresses a specific research question. The On-line Guide to Quality-of-Life Assessment¹⁵ is another database of existing HRQoL instruments. The US National Institutes of Health PROMIS Initiative¹⁶ has developed rigorously tested item banks across a broad range of domains and subdomains that allow comparisons. The PROMIS Initiative also actively evaluates methods to achieve brevity in instruments through different techniques. Many of these measures are publicly available through the PROMIS Assessment Center.¹⁷

Evaluating PROs as data sets

Although PRO assessment provides very rich information at the individual level, aggregating these data to measure performance of treatments and of the healthcare system delivering care at a target population level is challenging.⁹ One weakness, for example, is that results implied by patients in questionnaires or relayed by interviewers are outcomes based on patient's own

Current initiatives that include advanced analysis systems and predictive analytics are underway to improve data collection and statistical management of PROs at a population level.

assessment that may not be equivalent to particular concerns of most patients suffering the same disease.¹⁰ Individual patients may also decide when and with whom they share their health and disease-related information, which may impede usability and access to information. Thus, these and other social issues together with economic disparities must be overcome. Current initiatives that include advanced analysis systems and predictive analytics are underway to improve data collection and statistical management of PROs at a population level.¹⁸

In clinical research, PROs are most frequently the primary endpoint of observational studies. Their assessment have been shown to be paramount in generating information on situations where either exposing or preventing patients from receiving an intervention is unethical, but where it is conceivable to gather perspectives on the illness and to value patient preferences for other possible disease scenarios.¹ Furthermore, measuring PROs in observational studies is insightful in rare diseases. This is because reachable sample sizes are too small for conducting a clinical trial, but gathering primary data on patients' HRQoL and on the perceived

determinants of disease burden are very important for healthcare decision making.^{19,20}

How valuable is the assessment of PRO in healthcare?

In usual clinical practice, the differences between clinicians' and patients' understanding of the effect of disease (e.g., prevalence and severity of patients' symptoms, functional impairments, influence of disease on the individual's everyday life) and treatment have been extensively researched and reported.^{17,18,19} PROs bridge these discrepancies. Furthermore, patients' direct self-reporting on health problems facilitates the discussion of important symptoms and quality-of-life aspects with healthcare professionals. This supports documentation and can help to improve disease management and positively influence clinician decisions.¹⁻⁵

It is not surprising that a review of evaluations for approval of new pharmaceutical products by the EMA carried out between 1995 and 2003 showed more than a 30% increase in the use of HRQoLs and other PRO instruments, particularly in cancer-related treatments.²⁰ Similarly, about 24% of new drug approvals by the FDA between 2006 and 2010 in the US had PRO labelling.²¹ This figure rose to almost 77% between 2011 and 2015 as most approvals of new

Table 3. Other aspects to be considered in the selection of a PRO instrument

Aspects	What to ask
Documentation	Is/are there formal written documentation, publications on the use of the instrument (type of research, objectives and aims, limitations, findings)?
	Is there a user manual (how to administer it, score, interpret results)
Development	How was it developed? (methods and findings for content and concept development, validation in the original and other languages, robustness of validity, responsiveness and reliability findings)
Feasibility	Are the questions, tasks and scoring easily understandable?
	Is the mode of administration or data collection too long?
Target population	Is the scale suitable for the target population (very ill people, children, elderly)?
	Is there a need for a carer to help?
Language and cultures	Are translations properly validated?
Scoring	Is there a definition of the scoring procedure and is it easy to interpret?
Interpretation	Are guidelines for interpreting scale scores and dealing with missing data available?
License for use	Is there a fee attached to the use of the PRO instrument? (copyright protection, holders, extension)
	What are the conditions for using? (considering the number of projects to be conducted with the same instrument, number of subjects in whom the instrument will be used, period of time during which the instrument will be administered; clinical practice, academic, research, private, or public entities to run or support the project)

Note: Based on Gliklich et al.²⁶

products were made for diseases that traditionally rely on PROs for evaluating the benefits of treatment.²²

PRO data collection is increasingly integrated into clinical registries to produce real world data on the effectiveness of healthcare interventions.²³ The routine measurement of PRO has become more important to inform future care planning in a feasible and efficient manner.²⁴ Challenges in doing so, however, include selecting the most suitable PROs and PRO instruments, overcoming logistic hurdles of PRO collection, ensuring long-term sustainability and complete data gathering, controlling for selection bias and missing information, and managing data aggregation. In order to succeed, diverse stakeholders, including payers (e.g. insurance systems), policy-makers, clinicians, patients, and researchers should cooperate to eventually find valuable and meaningful data from the PROs collected in registries.²⁵

Conclusions

PROs are very useful for providing information about what patients think, how they feel, what their preferences are, and why they behave in the way they do towards their disease and treatment(s) especially in chronic, disabling, progressive, and other difficult-to-treat conditions. PROs may contain information little known to clinicians, policy makers, and regulatory authorities. These crucial data will help to determine the effectiveness and the success of treatments in usual clinical practice and real life. PROs are at the cornerstone for generating real world evidence and are a vital component of registries if these should be designed to eventually improve healthcare quality and information generation for decision making bodies. Appropriately selecting, measuring, interpreting, and reporting PRO data are fundamental.

References

- Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. *Pers Clin Res* 2011;2:137–44. [cited 2017 July 5]. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227331/#!po=6.25000>.
- Willke RJ. Measuring the value of treatment to patients: Patient-reported outcomes in drug development. *Am Health Drug Benefits* 2008;1:34–40.
- Food and Drug Administration. Guidance for industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims; 2009 [cited 2017 June 10]. Available from <https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf>.
- European Medicines Agency. Reflection paper on the use of patient reported outcome (PRO) measures in oncology studies, 2014 [cited 2017 June 10]. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500168852.pdf.
- McKenna SP. Measuring patient-reported outcomes: moving beyond misplaced common sense to hard science. *BMC Medicine*. 2011;9:86. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170214/pdf/1741-7015-9-86.pdf>.
- University of Oxford. Instrument Types. Patient Reported Outcomes Measurement Group;2017. [cited 2017 July 5]. Available from http://phi.uhce.ox.ac.uk/inst_types.php.
- Coons S, Gwaltney CJ, Hays RD et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (pro) measures: ISPOR ePRO Good Research Practices Task Force Report. *Value Health* 2009;12:419–29. Available from https://www.ispor.org/workpaper/patient_reported_outcomes/Coons.pdf.
- Dueck AC, Sloan JA. Meeting on the FDA draft guidance on patient-reported outcomes. *Value Health* 2007;10:S64–5.
- Frost MH, Reeve BB, Liepa AM, Stauffer JW, Hays RD; Mayo. FDA Patient-Reported Outcomes Consensus Meeting Group. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? *Value Health* 2007;10:S94–S105.
- Blinman P, King M, Norman R, Viney R, Stockler MR. Preferences for cancer treatments: an overview of methods and applications in oncology. *Ann Oncol* 2012;23 (5):1104–10.
- Cheung KL, Wijnen BFM, Hollin IL et al. Using best–worst scaling to investigate preferences in health care. *Pharmacoecoon* 2016;34:1195-1209.
- Kaplan RM, Frosch DL. Decision Making in medicine and health care. *Ann Rev Clin Psychol* 2005;1:525-56. Available from http://rmkaplan.bol.ucla.edu/Robert_M_Kaplan/2005_Publications_files/395-%20AnnRevClinPsych.pdf.
- Arnold D, Girling A, Stevens A, Lilford R. Comparison of direct and indirect methods of estimating health state utilities for resource allocation: review and empirical analysis. *BMJ*. 2009;339(b2):688. Available on <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2714630/>.
- ePROVIDE. Online support for clinical outcomes assessment; 2017. [cited 2017 July 5] Available from <http://www.proqolid.org/>.
- OLGA. The On-line Guide to Quality of Life Assessment; 2012 [cited 2017 July 5] Available from <http://www.olga-qol.com/>.
- Health Measures. PROMIS; 2017 [cited 2017 July 5] Available from <http://www.nihpromis.org/>.
- Morillas C, Feliciano R, Catalina PF, Ponte C, Botella M, Rodrigues J et al. Patients' and physicians' preferences for type 2 diabetes mellitus treatments in Spain and Portugal: a discrete choice experiment. *Patient Prefer Adherence* 2015;9:1443-58.
- Dilla T, Lizan L, Paz S, Garrido P, Avendaño C, Cruz-Hernandez JJ et al. Do new cancer drugs offer good value for money? The perspectives of oncologists, health care policy makers, patients, and the general population. *Patient Preference and Adherence* 2016; 10. Available from <https://www.dovepress.com/do-new-cancer-drugs-offer-good-value-for-money-the-perspectives-of-onc-peer-reviewed-article-PPA>.
- Flores LT, Bennett AV, Law EB, Hajj C, Griffith MP, Goodman KA. Patient-reported outcomes vs. clinician symptom reporting during chemoradiation for rectal cancer. *Gastroint Cancer Res* 2012;5: 119-24.
- Szende A, Leidy NK, Revicki D. Health-Related Quality of Life and other patient-reported outcomes in the European centralized drug regulatory process: a review of guidance documents and

performed authorisations of medicinal products 1995 to 2003. *Value Health* 2005;8: 534-48.

21. Gnanasakthy A, Mordin M, Clark M, DeMuro C, Sheri F, Copley-Merriman C. A review of patient-reported outcomes labels in the United States: 2006 to 2010. *Value Health* 2012;15:437-42.
22. Gnanasakthy A, Mordin M, Evans E, Doward L, DeMuro C. A review of patient-reported outcomes labeling in the United States (2011-2015). *Value Health* 2016;20:420-9.
23. Ashley L, Jones H, Thomas J et al. Integrating patient reported outcomes with clinical cancer registry data: a feasibility study of the electronic Patient-Reported Outcomes From Cancer Survivors (ePOCS) system. *J Med Internet Res* 2013;15:e230.
24. Franklin PD, Harrold L, Ayers DC. Incorporating patient-reported outcomes in total joint arthroplasty registries: challenges and opportunities. *Clin Orthop Relat Res* 2013;471:3482-8.
25. Doward LC, McKenna SP. Defining patient-reported outcomes. *Value Health* 2004;7: S4-8.
26. Gliklich RE, Dreyer NA, Leavy MB, editors. *Registries for Evaluating Patient Outcomes: A User's Guide* [Internet]. 3rd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014. Available from <https://www.ncbi.nlm.nih.gov/books/NBK208628/>.

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ICMJE to mandate data sharing statements

Those of us who attended the 2017 spring conference in Birmingham were treated to an excellent symposium on transparency in clinical trials, where EU Policy 0070¹ on disclosure of clinical data was a key focus. A month later, the ICMJE (International Committee of Medical Journal Editors) announced that beginning in July 2018 they will require that submitted manuscripts based on clinical trials carry a data sharing statement.² Data sharing statements will be expected to describe the following: whether data will be shared; what will be shared; and when and for how long the data will be available.³ Also, from 2019 new trials will have to include a data sharing plan in their registration information.

As the ICMJE themselves point out, these requirements – tellingly referred to as “*minimum requirements*” – do not mandate data sharing itself, only statements relating to data sharing. However, they warn that “editors may take into consideration data sharing statements when making editorial decisions” and that some journals “already maintain, or may choose to adopt, more stringent requirements for data sharing”.

Complementing the ICMJE’s *stick* approach, the authors of a recent Sounding Board article in the *New England Journal of Medicine* propose offering “data authorship” as a *carrot* to encourage data sharing.⁴ According to the proposal, people who gather clinical trial data should be given credit that can be used to support applications for tenure and funding. The hope is that this would serve as an incentive to share data with others.

References

1. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use). POLICY/0043. European Medicines Agency. 2010 Nov 30 [cited 2017 Jul 24]. Available from: http://www.ema.europa.eu/docs/envGB/document_library/Other/2010/11/WC500099473.pdf.
2. European Medicines Agency policy on publication of clinical data for medicinal products for human use. European Medicines Agency. 2014 Oct 02 [cited 2017 Jul 24]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf.
3. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A et al. Data sharing statements for clinical trials: A requirement of the International Committee of Medical Journal Editors. *PLoS Med* 2017;14:e1002315.
4. Bierer BE, Crosas M, Pierce HH. Data authorship as an incentive to data sharing. *N Engl J Med* 2017;376:1684–7.

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EMA releases the revised Good Pharmacovigilance Practices Module V

updated guidance on risk management plans



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Abstract

Recently, the EMA released the revised Module V – Risk Management Systems (Rev 2) of Good Pharmacovigilance Practices (GVP) accompanied by a revised version of the guidance on the format of the risk management plan (RMP) in the EU – in integrated format. The revision will result in concise, scientifically focussed and risk-proportionate documents and is applicable to all sections of the RMP, especially sections that have become overly lengthy over time and often duplicate information presented elsewhere in the dossier or in other documents, such as the periodic safety update report.

A changing environment

Since its beginning, pharmacovigilance (PV) has undergone continuous transformation. Legislation, guidelines, and processes have evolved over time to better ensure patient safety and improve monitoring of the safety of medicinal products. After releasing the Good Pharmacovigilance Practices (GVP) guideline¹ in 2012, the European Medicines Agency (EMA) committed to continuously improve the PV guidance based on stakeholder feedback and experience. Some GVP modules were revised to include clarifications or improvement of definitions and processes.² In parallel, a platform for regular dialogue with industry, the EMA-Industry stakeholder platform,³ was established, with regular meetings to provide updates and discuss specific topics, including risk management plans (RMPs). After publishing an initial revision in 2013, the EMA released a draft of Revision 2 of GVP module V⁴ on risk management systems and a draft version of the related RMP template⁵ for public consultation in February 2016. The guidance and template consultation resulted in a wide variety of stakeholder feedback from marketing authorisation holders, industry associations, national healthcare system representatives, and individuals, among many others. The main topics raised during the consultation phase included the definition and life cycle of safety concerns (important identified risk, important potential risk, and missing information), issues regarding inconsistencies between the different

parts and modules of the RMP, and other technical issues and questions surrounding duplication of information provided in the RMP and other safety summary documents.

The final guidance,⁶ released at the end of March 2017, set a new milestone in the process of continuous improvement of the RMP guidance. The new RMP template⁷ is a straightforward, well-structured document that medical writers can easily use to prepare RMPs, and the concepts behind risk management have been clarified and adjusted to better reflect the stages of the life cycle of a medicinal product. Understanding these principles and the expectations of the revised guidance is crucial to prepare and manage RMPs that effectively identify the risks of a medicinal product and lead to appropriate safety decisions, thus, better ensuring patient safety.

Revision 2: What has changed?

Besides streamlining the guidance text by removing duplications within the RMP modules and with other guidance documents, Revision 2 of GVP module V addresses most of the areas for improvement that had been identified during previous consultations with industry.^{6,8} An intrinsic challenge of RMPs was to determine the safety concerns: important identified risks, important potential risks, and missing information. In addition, the role of the RMP as a planning document was not clearly linked to the

Table 1. Clarifications of terminology in GVP module V Revision 1 and Revision 2

Term	GVP module V Revision 1 ⁸	GVP module V Revision 2 ⁶
Identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest	Undesirable clinical outcomes for which there is sufficient scientific evidence that they are caused by the medicinal product
Potential risk	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed	Undesirable clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal
Important identified risk and important potential risk	An identified risk or potential risk that could have an impact on the benefit-risk balance of the product or have implications for public health	The RMP should focus on the important identified risks that are likely to have an impact on the risk-benefit balance of the product. An important identified risk to be included in the RMP would usually warrant: <ul style="list-style-type: none"> ● Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk); ● Risk minimisation activities: product information advising on specific clinical actions to be taken to minimise the risk, or additional risk minimisation activities. The important potential risks to be included in the RMP are those important potential risks that, when further characterised and if confirmed, would have an impact on the risk-benefit balance of the medicinal product
Missing information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant	Gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far

Source: GVP module V Revision 1 and GVP module V Revision 2^{6,8} Abbreviations: GVP, good pharmacovigilance practices; PV, pharmacovigilance; RMP, risk management plan

life cycle of the medicinal product. The main questions asked in stakeholder meetings and consultations between the EMA and industry can be summarised as follows:

- What should be considered relevant for inclusion in the safety specification (Part II) of the RMP? (What is “important”? When is missing information relevant for inclusion in the RMP?)
- How should important risks be defined and characterised? (For example, can “off-label use in children” be defined as an important potential risk? Should an adverse clinical outcome be defined?)
- How should the safety concerns evolve through the life cycle of the medicinal product? (What is the expectation of the EMA and the national authorities?)

Clear premises

GVP module V Revision 2 provides some more specific wording and clarifications for the definition of identified and potential risks,

missing information, and important risk. Further guidance was added to provide a pragmatic approach while applying definitions.

As already specified in Revision 1,⁸ the RMP should still focus on those risks that are relevant for the risk-benefit balance of the medicinal product. Revision 2 clarifies that risks should be identified through adverse clinical outcomes that are caused by the use of a medicinal product (identified risks) or that might be caused by the use of a medicinal product (potential risks). For example, if off-label use in children is considered an important potential risk for a medicinal product, the potentially associated adverse clinical event should be defined. With regard to missing information, the focus is on a potential different safety profile in certain situations or populations as compared to the known safety profile.

The definition of important risk is still based on the impact on the risk-benefit balance of the medicinal product, but it is now also linked to the need for further evaluation through PV activities

(important identified and potential risks) or to the need for management through risk minimisation measures (important identified risks).

A key aspect of GVP module V Revision 2 is the evidence supporting identification of important (identified and potential) risks and missing information. In line with this, Module SVII now includes sections to discuss the evidence for defining, re-classifying, or removing safety concerns.

Table 1 compares the definitions provided in GVP module V Revision 1 and Revision 2.

Less is more

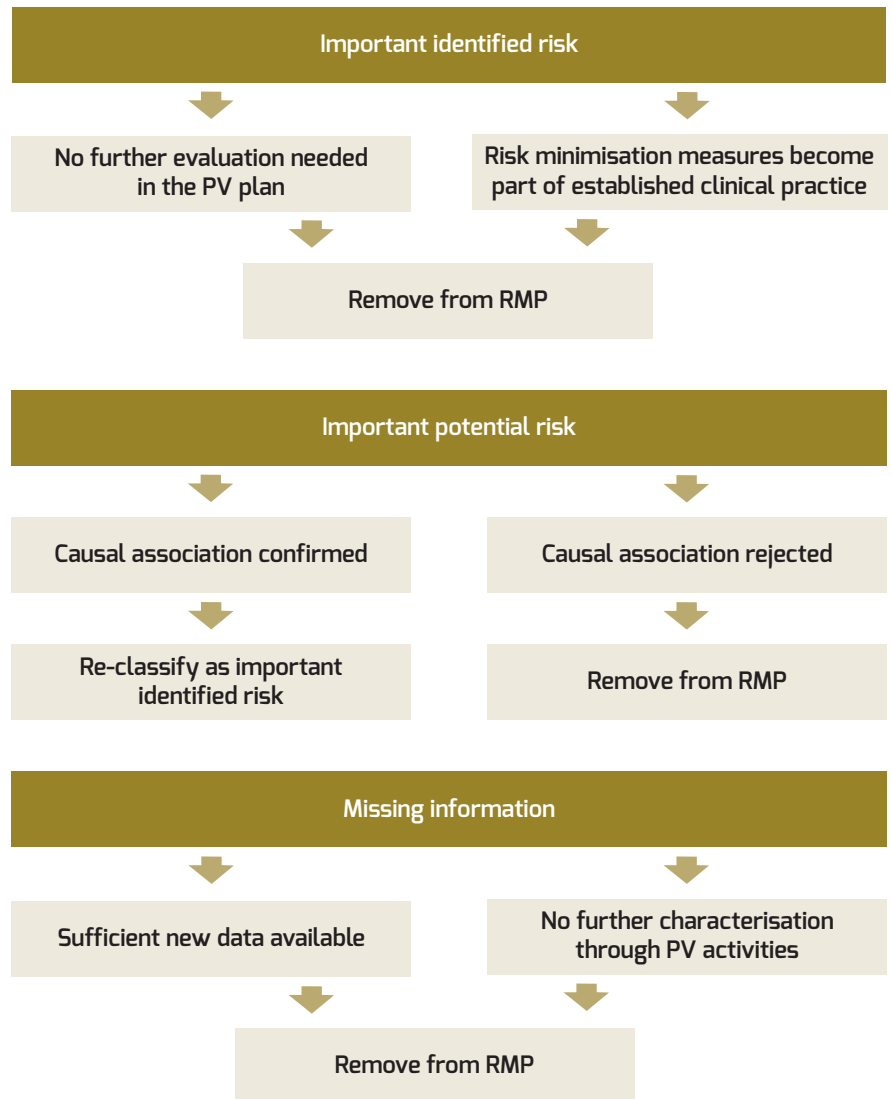
Another challenge when preparing RMPs was how to integrate safety information gathered over time, what to focus on, and how increasing knowledge should support changes in the RMP. In GVP module V Revision 2, the purpose of the RMP is redefined to strengthen the concept of risk proportionality. The amount of information expected to be provided in the safety specification of the RMP varies depending on the stage

of the medicinal product life cycle and the need for post-authorisation data. For initial marketing authorisation applications, a full RMP needs to be submitted, whereas for products with an established safety profile and post-marketing knowledge (e.g. generic drugs, fixed-drug combinations with no active substance, and well-established products), most modules of the safety specification can be omitted.

Similarly, according to the principle of risk proportionality, knowledge regarding a medicinal product's safety profile are expected to increase and safety concerns are expected to evolve as a product proceeds through its life cycle. GVP module V Revision 2 provides guidance on the post-authorisation removal of safety concerns and encourages marketing authorisation holders to critically revise the list of safety concerns and the associated PV activities and risk minimisation measures during the post-marketing phase. In particular, the list of safety concerns will change over time as knowledge regarding the product's safety profile increases, thus confirming or refuting a causal association with the medicinal product (see Figure 1). In addition, PV activities and risk minimisation measures can also change over time (e.g. when studies are either newly planned or completed or when risk minimisation measures are either integrated in clinical practice or shown to be ineffective). Therefore, the requirement for submission of RMP updates is linked to significant changes in the list of safety concerns, the PV plan, and/or the risk minimisation plan.

Moving forward: What's next?

The RMP prepared according to GVP module V Revision 2 is more focussed on those risks that are relevant to the risk-benefit balance of the medicinal product, and which need further evaluation (PV activities) and/or management (risk minimisation activities). The amount of information provided should be risk-proportionate, and the RMP is expected to evolve during the life cycle of the medicinal product. Although general understanding of the revised guidance, as well as individual opinions shared by members of the Pharmacovigilance Risk Assessment Committee (unpublished), clearly point towards the need for critical review of the list of safety concerns during the life cycle of a medicinal product, the question remains as to whether marketing authorisation holders will deem the available evidence sufficient for a



Abbreviations: PV, pharmacovigilance; RMP, risk management plan

Figure 1. Expected changes over time in the list of safety concerns according to GVP module V Revision 2.⁶

critical review, and whether the assessors will agree on the proposed changes. The next phase of the life cycle of the RMP guidance has started, and we can expect further clarifications and adjustments in the future, based on increasing experience with Revision 2 and continuing dialogue between the EMA and industry stakeholders.

Conclusion

Revision 2 of GVP module V will result in shorter RMPs. Most sections on risks that are not classified as “important” have been removed, and the section on post-marketing experience has

been reduced to the presentation of post-authorisation exposure to avoid redundancies with the periodic safety update report. Once implemented, the clarifications about safety concerns will hopefully lead to a smoother RMP update process and, in the long run, fewer important risks that have to be managed in the RMP. This can be the actual breakthrough of the revision, if it leads to RMPs that do not overwhelm the reader with information and data on risks that are already provided in many other documents, but that instead focus on the issues of their original intent. These issues are identifying or characterising the safety profile of

the medicinal product, indicating how to further characterise its safety profile, and documenting measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those measures.

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Conflicts of Interest and Disclaimers

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References

1. Good pharmacovigilance practices. European Medicines Agency. [cited 2017 Jun 12]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp.
2. Guidelines on good pharmacovigilance practices (GVP). Introductory cover note, last updated with draft revision 2 of module V on risk management system for public consultation. EMA/136477/2016. 2016 Feb 29 [cited 2017 Jun 12]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/03/WC500224566.pdf.
3. European Medicines Agency's interaction with industry stakeholders. Annual Report 2015. EMA/774549/2015. 2016 Jun 16 [cited 2017 Jun 12]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/06/WC500208988.pdf.
4. Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2) – draft for public consultation. European Medicines Agency and Heads of Medicines Agencies. 2016 Feb 24 [cited 2017 Jun 12]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/02/WC500202424.pdf.
5. Draft guidance on format of the risk management plan (RMP) in the EU – in integrated format. EMA/PRAC/613102/2015 Rev.2 accompanying GVP Module V Rev.2. European Medicines Agency. 2016 Feb 29 [cited 2017 Jun 12]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500202373&mid=WC0b01ac058009a3dc.
6. GVP Module V–Risk management systems, EMA/838713/2011 Rev 2. European Medicines Agency and Heads of Medicines Agencies. 2017 Mar 28 [cited 2017 Jun 12]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf.
7. Guidance on format of the risk management plan (RMP) in the EU – in integrated format. European Medicines Agency and Heads of Medicines Agencies. 2017 Mar 30 [cited 2017 Aug 18]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/03/WC500224770.docx.
8. Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 1). European Medicines Agency and Heads of Medicines Agencies. 2014 Apr 15 [cited 2017 June 12]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf.

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Mentoring tomorrow's medical writers

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Abstract

Mentoring may be valuable to today's students who are considering their future career options in an increasingly competitive, demanding, and challenging world. This article outlines the author's experience of mentoring tomorrow's medical writers, provides examples of the topics discussed in mentoring sessions, and describes the skills required to provide effective support. A successful mentoring relationship can provide developmental benefits for both mentor and mentee.

In the December 2016 issue of *Medical Writing*, I described speaking at a local careers event, which resulted in an invitation to join the University of East Anglia student mentoring programme. Since then, I have started to mentor students who are considering their future career options.

What is the mentoring programme?

The objective of the programme is to provide career-focussed mentoring for current students and recent graduates. Establishing a graduate-level career is competitive, demanding, and challenging, and the programme recognises that professional experience and insight can be a considerable asset.

The university uses the following definition of mentoring according to Alred & Garvey:¹

A process in which a more skilled or more experienced person, serving as a role model, teaches, sponsors, encourages, counsels and befriends a less skilled or less experienced person for the purpose of promoting the latter's professional and/or personal development. Mentoring functions are carried out within the context of an ongoing, supportive relationship between the mentor and mentee.

Students are matched with a suitable mentor for two types of support:

- **Insider Insight mentoring:** Information sessions designed to give a student a greater insight into a particular career sector or business area.
- **Six-month mentoring:** A student receives advice and guidance through one-to-one sessions over 6 months, with the aim of helping them to broaden their horizons and be guided to their first steps into employment.

Mentors are supported with various resources, e.g., a handbook, online training

modules, newsletters, and a LinkedIn group. Regular networking events take place with students, mentees, mentors, and the university careers staff. Face-to-face meetings on the university campus are encouraged, with other contact via telephone, email, Skype or LinkedIn, as appropriate.

Who do I mentor and what does it involve?

So far, I have been matched with several students for Insider Insight sessions. These have been with students in different years (first year to final year) and studying various subjects (including biological sciences, biochemistry, English literature, and creative writing). I've also spoken to members of research staff who are considering possible roles outside academia. Although every session has been different, each one included plenty of stimulating questions from the mentee.

To give an idea of the types of topics covered, I have been asked to:

- Explain the different types of medical writing activities
- Summarise a typical day as a medical writer (Is there one?)
- Talk about core competencies and skills, e.g. analytical, scientific, language, and writing
- Describe different work environments and motivations in the pharmaceutical industry
- Advise on speculative job applications and medical writing tests
- Provide input into making a curriculum vitae as attractive to an employer as possible
- Give tips on managing projects

- Help with networking techniques and becoming more assertive
- Discuss challenges and successes in my career
- Describe the differences, benefits, and challenges of being an employee versus a freelancer.

Each conversation required me to listen carefully, ask effective questions, and encourage the mentee to think about solutions and to take ownership of possible actions. These are all skills that medical writers often use when collaborating with document contributors and reviewers, but they apply to effective mentoring too. I also try to provide direction with regard to the mentee's particular questions and interests, pointing them towards other available resources if appropriate. We often discuss skills acquired during a degree course or academic research that could be transferred to a medical writing career and also consider new skills that may need to be developed.

What am I learning from the mentoring experience?

Mentoring provides a new challenge for me. It not only allows me to help a student recognise his or her skills, but it also means I can revive and develop skills I have acquired previously. As a freelance medical writer with a career background in managing clinical data, staff, and human resources, skills such as objective setting,

So if you are an aspiring medical writer, why not consider finding a mentor who could provide insights into our rewarding profession and help you “get your foot in the door”?

providing feedback, and interviewing techniques are now proving useful in a different setting.

The opportunity to network with other mentors from diverse business areas is developing my confidence as a freelance professional, outside of the medical writing community. Although I am involved in the programme primarily to “give something back” by sharing

knowledge and experience to inspire and support others, it provides an opportunity to create a link with my local university.

Could a mentor be of benefit to you?

Mentoring can be of benefit to many people with different levels of knowledge and experience. If you think a mentor may be useful to you, it is not necessary to be part of an organised mentoring programme – you probably know at least one person who may be willing to mentor you.

So if you are an aspiring medical writer, why not consider finding a mentor who could provide insights into our rewarding profession and help you get your foot in the door?

Or if you already have medical writing experience, why not think about offering to mentor someone who might benefit from your knowledge? Or why not consider finding a

mentor to help you further your own professional or personal development?

In the short time that I have been part of the university programme, I have already seen that a mentee-mentor relationship can be a mutually rewarding experience, and I look forward to continuing to mentor students in the new academic year. As noted in *The Mentoring Pocketbook*,

“Mentoring is probably the most powerful developmental process people can experience. And when it works, it develops two for the price of one.”¹.

Conflicts of interest

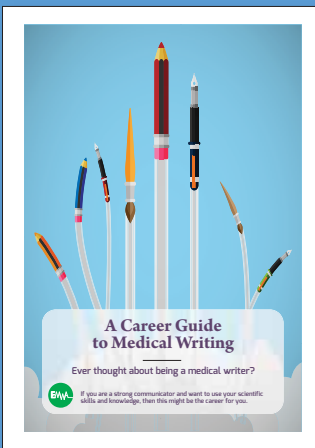
The author declares no conflicts of interest.

References

1. Alred G, Garvey B. The mentoring pocketbook. 3rd ed. Alresford: Management Pocketbooks Ltd; 2010.

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EMWA's New Medical Writing Career Guide is now available!

Included in the guide:

- What is medical writing
- The different types of medical writing
- The skills and qualifications needed to be a medical writer
- Where medical writers work and what they do
- How to get started
- How much to expect to get paid
- Career prospects for medical writers

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

New guidance and process improvement for periodic safety update reports

April, 6, 2017 – Following two years of experience with safety monitoring of nationally authorised medicines via the single assessment of periodic safety update reports (PSURs), the EMA has issued additional guidance and recommendations as part of its commitment to continuous process improvement. Two new documents aim at improving the safety information and benefit-risk assessment of medicines in the context of the periodic safety update single assessment (PSUSA): *Explanatory note to GVP Module VII* and *Assessors' questions and answers (Q&A) guidance on PSUR single assessment (PSUSA)*.

PSURs are reports that evaluate the benefit-risk balance of a medicine as evidence is gathered in clinical use. They are submitted by marketing authorisation holders at defined time points following a medicine's authorisation. The agency uses the information in PSURs to determine if there are new risks linked to a

medicine or if the balance of benefits and risks of a medicine has changed. Based on this information, EMA decides whether further investigations are needed or whether measures have to be taken to protect public health. If medicinal products contain the same active substance or the same combination of active substances, the related PSURs will be jointly assessed in a single assessment procedure.

The agency has carried out single assessments of PSURs for nationally authorised medicines containing the same active substances or combinations of active substances since 2015. Before that, PSURs for medicines containing the same active substance or the same combinations were submitted for assessment by their respective marketing authorisation holders to different national competent authorities at different times. The introduction of single assessments helped to streamline the process and to ensure that all the evidence generated about medicines containing

the same active substance is reviewed at the same time by one authority, resulting in consistent safety information.

The PSURs submitted by marketing authorisation holders are assessed by EMA's Pharmacovigilance Risk Assessment Committee together with a leading assessor from one nominated national authority for medicines regulation, the so-called lead Member State. The recommendations made during the assessment are legally binding, applicable to all Member States and implemented across the EU. The joint assessment helps to optimise use of resources between national competent authorities.

Single assessments of PSURs are a key post marketing regulatory tool to ensure patients receive up-to-date information on the safety of medicines. PSURs provide regular opportunities for monitoring medicines in a public health space that covers nearly 500 million people.

Reporting irregularities that may affect medicines

April 10, 2017 – The European Medicines Agency's (EMA) Management Board has adopted a new policy on how EMA handles allegations of improprieties received from external parties. These improprieties may include allegations of departures from standards of good practices that could have an

impact on the evaluation and supervision of medicines. The goal is to create an environment where individuals from outside the agency feel confident to raise their concerns on improprieties in their area of work. The policy helps EMA assess these reports and coordinate any further investigation in a structured way, while protecting the confidentiality of the reporter.

A dedicated email inbox, reporting@ema.europa.eu, has been created. Individuals external to EMA can raise their concerns by sending a message or providing information to this address. They can also send a letter to the agency. Their identity will be kept confidential.

If the allegations concern a centrally authorised medicine, EMA will coordinate the investigation. If there are any concerns that the improprieties may affect the balance of benefits and risks of the medicine, EMA's scientific committees may consider regulatory action. If the allegations concern a nationally authorised

medicine, EMA may, on a case-by-case basis, refer the matter to the national medicines agency in the European Union (EU) Member State where the concerned medicine is authorised. If there is a suspicion that fraud is involved, EMA will transmit the report to the European Anti-Fraud Office (OLAF) in accordance with the existing arrangements between the two institutions.

Since 2013, EMA has received a total of 43 reports that relate, for example, to the manufacturing of medicines or the conduct of clinical trials. Although no formal policy has existed until now, all reports were dealt with in line with the principles included in the new policy.

The policy was adopted by the Management Board at its March meeting and came into effect on 17 March 2017. It was prepared in consultation with the European Commission and OLAF.



New guide on biosimilar medicines for healthcare professionals

May 5, 2017 – The EMA and the European Commission have published an information guide for healthcare professionals on biosimilar medicines. Biosimilars are biological medicines that are highly similar in all essential aspects to a biological medicine that has already been authorised. The objective of the guide is to provide healthcare professionals with reference information on both the science and regulation underpinning the use of biosimilars.

The guide is a joint initiative of EMA and the European Commission. It was developed in collaboration with EU scientific experts, in response to requests from healthcare professionals. Organisations from across the EU representing doctors, nurses, pharmacists and patients have also shared useful views, to ensure that the guide adequately addresses questions relevant to healthcare professionals.

The guide was launched on 5 May 2017 at the European Commission's third stakeholder event on biosimilar medicines, a discussion

forum that provides a platform for stakeholders interested in biosimilars, including healthcare professionals, patients, payers, regulators, and industry.

The EU has pioneered the regulation of biosimilar medicines by establishing a solid framework for their approval and by shaping biosimilar development globally. Since the EU

approved the first biosimilar in 2006, the evidence gained from clinical experience shows that biosimilars approved in the EU are as safe and effective in all their approved indications as other biological medicines. To date, the agency's Committee for Medicinal Products for Human Use (CHMP) has recommended 28 biosimilars for use in the EU.



Green light given for the new EudraVigilance system for collection and monitoring of suspected adverse reactions

May 25, 2017 – The EMA will launch a new and improved version of EudraVigilance, the European information system of suspected adverse reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA). The new version of EudraVigilance will go live on 22 November 2017 with enhanced functionalities for reporting and analysing suspected adverse reactions.

Users of the system, i.e. national competent authorities, marketing authorisation holders and sponsors of clinical trials, have to make final preparations to ensure that their processes and local IT infrastructure are compatible with the new system and the internationally agreed format. The EMA will support national competent authorities, marketing authorisation holders and sponsors of clinical trials in the EEA through targeted e-learning and face-to-face trainings, webinars and information days.

The enhancements for reporting and analysing suspected adverse reactions of the new EudraVigilance system will support better safety monitoring of medicines and a more efficient reporting process for stakeholders.

Expected benefits include:

- Simplified reporting of individual case safety reports (ICSRs) and the re-routing of ICSR reports to Member States as marketing authorisation holders will no longer have to provide these reports to national competent authorities, but directly to EudraVigilance, which will ultimately reduce duplication of efforts. An ICSR provides information on an individual case of a suspected adverse reaction to a medicine;
- Better detection of new or changing safety issues, enabling rapid action to protect public health;
- Increased transparency based on broader access to reports of suspected adverse reactions by healthcare professionals and general public via the adrreports.eu portal, the public interface of the EudraVigilance database;
- Enhanced search and more efficient data analysis capabilities;
- Increased system capacity and performance to support large volumes of users and reports (including non-serious adverse reactions originating from the EEA);

More efficient collaboration with the World Health Organisation (WHO) as EMA will make the reports of individual cases of suspected adverse reactions within the EEA available to the WHO Uppsala Monitoring Centre directly from EudraVigilance; Member States will no longer need to carry out this task.

The reporting of adverse reactions by patients and healthcare professionals to national competent authorities based on local spontaneous reporting systems will remain unchanged. There will also be no changes to the reporting of suspected unexpected serious adverse reactions during clinical trials until the application of the new Clinical Trial Regulation.



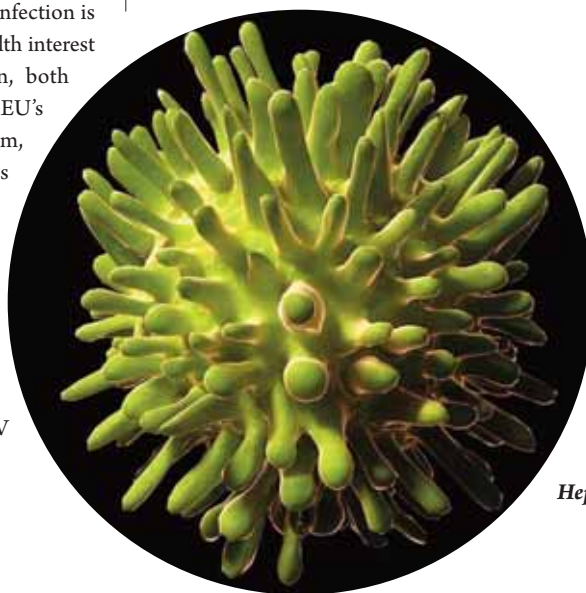
Two new medicines evaluated under accelerated assessment recommended for the treatment of chronic hepatitis C

June 23, 2017 – The EMA has recommended granting marketing authorisations in the EU for Maviret and Vosevi, two new medicines indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Hepatitis C virus infection is a major public health challenge. It affects between 0.4% and 3.5% of the population in different EU Member States and is the most common single cause of liver transplantation in the EU. Approximately 15 million people are chronically infected with HCV throughout Europe. As HCV infection is considered to be of major public health interest in terms of therapeutic innovation, both medicines were evaluated under the EU's accelerated assessment mechanism, which aims to speed up patients' access to new medicines where there is an unmet medical need. Maviret and Vosevi are the first medicines for which accelerated assessment has been carried out within 120 days.

Maviret and Vosevi belong to the direct acting antivirals that block the action of proteins essential for HCV

replication. This type of medicine achieves high cure rates of the infection and does not require the concomitant use of interferons, medicines which are associated with poor tolerability and potentially serious side effects. Both Maviret and Vosevi are active against all genotypes of the virus and, with some differences between the two medicines, may be specifically useful in some patients who failed or cannot use previously available therapies.



Hepatitis C

The effects of Maviret were studied in a total of 2,376 patients who participated in eight pivotal and three supportive clinical trials, and the effects of Vosevi were studied in over 1700 patients in four main clinical trials. The HCV could no longer be detected in over 90% of patients 12 weeks after the end of treatment with either drug. If the blood of patients is clear of HCV for more than 12 weeks they are generally considered as being cured of the infection. Adverse events reported with Maviret were generally mild, including headache, fatigue, diarrhoea, nausea and abdominal pain. With Vosevi, mild nausea, headache and diarrhoea were the most common side effects; other potentially related adverse effects were decreased appetite, vomiting, muscle spasms, and rash.

The opinions adopted by the CHMP at its June 2017 meeting are an intermediary step on Maviret's and Vosevi's path to patient access. The CHMP opinions will now be sent to the European Commission for the adoption of decisions on EU-wide marketing authorisations through an accelerated procedure.

Probiotic Symbioflor 2 recommended for continued use in the treatment of irritable bowel syndrome but not of other gastrointestinal disorders

June 23, 2017 – A review by the EMA has concluded that the probiotic Symbioflor 2 and associated names can continue to be used for treatment of irritable bowel syndrome (IBS) in adults. However, the medicine should no longer be used more widely to treat so-called functional gastrointestinal disorders, a group of



disorders with a variety of causes that may require different treatment approaches.

Symbioflor 2, which contains *Escherichia coli* bacteria, has been described as a probiotic, which means that it encourages the growth of beneficial organisms (flora) in the gut. It was first made available in Germany in the 1950s and subsequently in Austria and Hungary.

In reaching its conclusions, EMA's Committee for Medicinal Products for Human Use (CHMP) reviewed all available evidence on the effectiveness and safety of Symbioflor 2. The data included clinical studies, scientific publications, post marketing experience, as well as information provided by the company and the views of an expert group formed for evaluating Symbioflor 2. The review did not find any new evidence on the effectiveness of Symbioflor 2 since the product was last approved. Available evidence

suggests that the risk of harm from Symbioflor 2 is low. Benefit has not yet been established in children with IBS.

Since the available data are not sufficiently robust for the CHMP to draw conclusions on how well Symbioflor 2 works and whether it is effective for any particular type of IBS, the CHMP has asked the company to carry out a well-designed study on effectiveness and safety among patients with different features of IBS (e.g. those with diarrhoea or with constipation as an important feature). Submission of the study report to national authorities will be a condition for maintaining Symbioflor 2's marketing authorisation. The CHMP recommendation will now be sent to the European Commission for a legally binding decision that will be valid throughout the EU.

Journal Watch

Journal Watch is based on the French-language blog *Rédaction Médicale et Scientifique*, by Hervé Maisonneuve available at www.redactionmedicale.fr.

SECTION EDITOR



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Data sharing is encouraged by institutions and journals: Authorship of “shared” papers should be clear

When researchers share data, the teams analysing them want to publish their results. How should authorship of publications be defined? Who are the authors – the researchers who collected and then shared the data and/or those who analysed the data? Conflicts among researchers are frequent when it comes to listing authors. The issue is important to researchers as they seek advancement, apply for grants, etc.

In the *New England Journal of Medicine*, Bierer et al propose that the persons who contributed to the generation of data should be named “data authors,” with their names added to the byline. Data authors are responsible for the integrity of the data set but not responsible for the scientific or clinical conclusions. A manuscript could have distinct data authors and authors whose primary contribution has been to perform data analysis of an existing data set. Five situations have been identified to allocate credit for data sharing and tracing the data set; many questions are not yet



answered. Authors and journal editors should try to implement these suggestions and then work to improve the classification.

Reference

Bierer BE, Crosas M, Pierce HH. Data authorship as an incentive to data sharing. *N Engl J Med* 2017; 376:1684–7.

The CLUE recommendations: Cooperation and Liaison between Universities and Editors: a preprint submitted for discussion

There is a need for guidelines proposing how to improve collaboration between universities and journal editors. A preprint with recommendations by 14 internationally prestigious authors was posted on May 19, 2017; it is open for comments from researchers, editors, and other interested parties. We should all consider



participating in this open peer review. The guidelines were discussed at a workshop held at the World Conference on Research Integrity at the end of May 2017 in Amsterdam, but the allotted time did not permit all ideas to be discussed.

The authors of the preprint recommend the following:

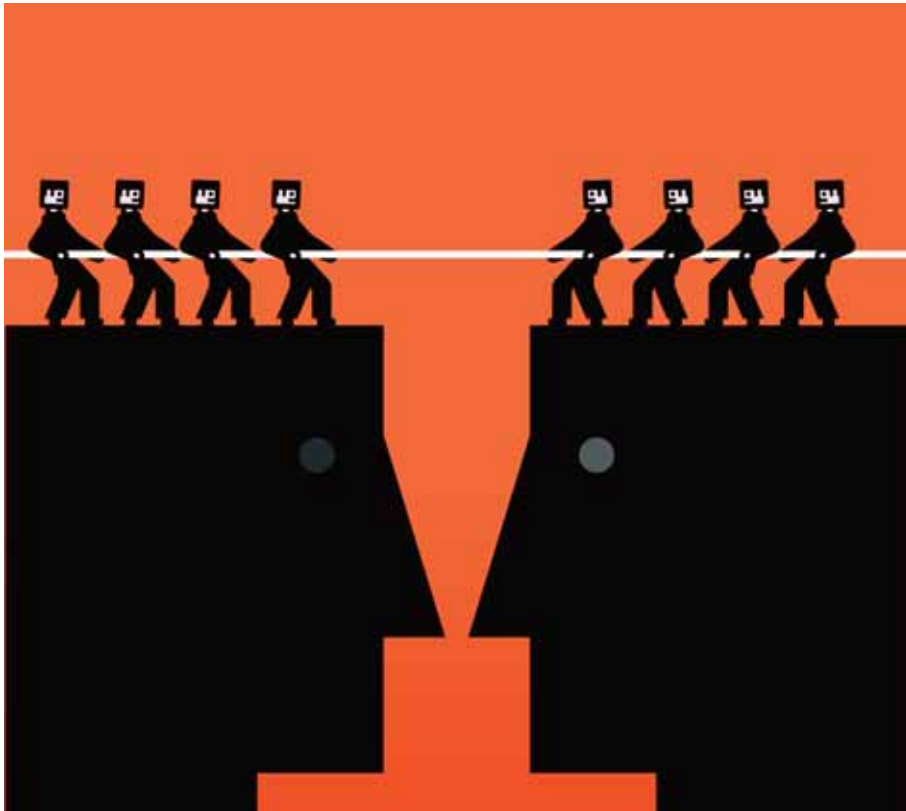
- National registers of individuals or departments responsible for research integrity at institutions should be created;
- Institutions should develop mechanisms for assessing the validity of research reports that are independent from processes to determine whether individual researchers have committed misconduct;
- Essential research data and peer review records should be retained for at least 10 years;
- While journals should normally raise concerns with authors in the first instance,

they also need criteria to determine when to contact the institution before, or at the same time as, alerting the authors in cases of suspected data fabrication or falsification to prevent the destruction of evidence;

- Anonymous or pseudonymous allegations made to journals or institutions should be judged on their merit and not dismissed automatically;
- Institutions should release relevant sections of reports of research trustworthiness or misconduct investigations to all journals that have published research that was the subject of the investigation.

Reference

Wager E, Kleinert S, Garfinkel M et al. Cooperation and liaison between universities and editors (CLUE): recommendations on best practice. *BioRxiv* May 2017
<https://doi.org/10.1101/139170>.



Conflict of interest and all aspect of medical sciences

A recent theme issue of *JAMA* is dedicated to the topic of conflicts of interest (COI) and includes 23 scholarly viewpoints, and two research reports.¹ I suggest consulting the table of contents and reading the three editorials, titled “The complex and multifaceted aspects of conflicts of interest”, “Conflict of interest and medical journals”, and “Reconsidering physician-pharmaceutical industry relationships”. This issue covers COIs from numerous perspectives:

academic medical centres, health care professionals, industries, journal editors and reviewers, patients, and public. Disclosing COI is critical if physicians are to retain the trusts that patients have placed in the profession. Many institutions and universities have established policies to report COIs. All COI aspects are presented: opinion leaders, medical school, industry, continuing medical education, and guidelines development.

The issue has two interesting original contributions with the following conclusions:

- According to data from 2015 Open Payments reports, 48% of US physicians were reported to have received a total of \$2.4 billion in industry-related payments, primarily general payments, with a higher likelihood and higher value of payments to physicians in surgical vs primary care specialties and to male vs female physicians.²
- Implementation of policies at US academic medical centres that restricted pharmaceutical representative sales visits to physicians (“detailing”) between 2006 and 2012 was associated with modest but significant reductions in prescribing of detailed drugs across 6 of 8 major drug classes; however, changes were not seen in all academic medical centres that enacted policies.³

You can listen to an audio summary of the issue by *JAMA* Editor-in-Chief Howard Bauchner, MD, at <http://jamanetwork.com/learning/audio-player/14374325>.

References

1. Conflict of interest [theme issue]. *JAMA*. 2017;317.
2. Tringale KR, Marshall D, Mackey TK et al. Types and distribution of payments from industry to physicians in 2015. *JAMA*. 2017;317(17):1774–1784.
3. Larkin I, Ang D, Steinhart J et al. Association between academic medical center pharmaceutical detailing policies and physician prescribing. *JAMA*. 2017;317:1785–95.

Save the date

The 45th EMWA Conference in Cascais, Portugal
2-4 November 2017

For more information: http://www.emwa.org/EMWA/Conferences/Future_Conferences/EMWA/Conferences/EMWA_Future_Conferences.aspx

Communicating science effectively to the public is a complex task in a competitive environment

The Academy of Medical Sciences (UK) published a report¹ that confirmed a problem as stated by Freer and Godlee: “Only one in three members of the public trusts the results of research... More than four-fifths of general practitioners and two-thirds of British adults disbelieved the results of trials funded by the drug industry.”² Is it limited to the UK? I think that we can generalise this observation. Could it be worse in other countries? The report has 12 recommendations that are reprinted in a *BMJ* editorial:

1. Involve patients, carers, and the public in research.
2. Address gaps in training in research methods and statistics.
3. Enhance the recognition of robust research findings.
4. Ensure best use is made of new sources of evidence.
5. Publish research findings.
6. Develop frameworks for declaring and managing interests.
7. Develop best practice guidelines for academia-industry relationships.
8. Improve the content of patient information leaflets.

9. NHS Choices should be a central repository of information on the benefits and harms of medicines.
10. Improve the reporting of scientific evidence in the media.
11. Support joint decision making between healthcare professionals and patients.
12. Continue dialogue and engagement with patients and the public.

The recommendations are detailed in 7 pages of the 116-page report. The media debates about the use of statins to prevent cardiovascular disease, Tamiflu to treat flu, and the HPV vaccine to prevent cervical cancer are used as case reports illustrating the need to better communicate science to the public. Recommendation 10 confirms that we must better understand the reporting of the scientific process.

These observations are probably similar for most of the scientific debates such as climate, food, genetically modified organisms, etc. Communicating science effectively is a complex task and is not obvious in a competitive environment. A report from the National Academies of Sciences, Engineering, and Medicine (USA) showed that we need more

research to understand how to better communicate science to the public.³ The scientists tend to deliver evidence when the public has personal values and beliefs. Scientific findings and evidence can conflict with core human values, religious beliefs, interests, and long-held views. Emerging science raises ethical or political questions that science itself cannot resolve.

References

1. Academy of Medical Sciences. Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines. 2017. <https://acmedsci.ac.uk/file-download/44970096>.
2. Freer J, Godlee F. Judging the benefits and harms of medicine. Only thrustworthy evidence will earn the public's trust. *BMJ* 2017;357:j3129.
3. National Academies of Sciences, Engineering, and Medicine. Communicating science effectively: A research agenda. Washington, DC: The National Academies Press. 2017. doi: 10.17226/23674.

Transparency in authors' contributions and responsibilities

The president of the National Academy of Sciences, Marcia McNutt (former editor of *Science* journals) convened a group from leading journals and scientific organisations at a retreat in February 2017. The objective was to discuss how to promote standards that would increase transparency in author contributions to research papers. The outcome was a preprint that was posted online on May 20, 2017; commentaries are welcome.

They proposed to adapt the International Committee of Medical Journal Editors (ICMJE) statement as follows:

Each author is expected to have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND has approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND agrees to be personally accountable for the author's own contributions and for ensuring that

questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

There are numerous proposals that merit attention. They recommended that journals adopt common and transparent standards for authorship (see above), outline responsibilities for corresponding authors, adopt the CRediT (Contributor Roles Taxonomy) methodology for attributing contributions, include this information in article metadata, and encourage authors to use the digital persistent identifier ORCID. Research institutions should have regular open conversations on authorship criteria and ethics. Funding agencies should adopt ORCID and accept CRediT. Scientific societies should further promote authorship transparency by implementing these recommendations through their meetings and publications programs.

CRediT (<http://docs.casrai.org/CRediT>) has been implemented by a few journals; it defines the following contribution roles performed in the work leading to a published



research article: conceptualisation, methodology, software, validation, formal analysis, investigation, resources, data curation, writing/original draft preparation, writing/review and editing, visualisation, supervision, project administration, and funding acquisition.

Reference

- McNutt M, Bradford M, Drazen J et al. Transparency in authors' contribution and responsibilities to promote integrity in scientific publication. *BioRxiv*, May 20, 2017 doi: <http://dx.doi.org/10.1101/140228>.

Getting Your Foot in the Door

Editorial

In this edition of GYFD, EMWA Internship Forum (IF) lead **Derek Ho** gives us a rundown on the second *Live IF* in Birmingham. Don't forget – Barcelona is the next IF venue!

The second contribution is from **Laura Rodriguez**. Laura is not a medical writer and she did not get her current internship position in big pharma through IF. But the powerful piece she shares with us speaks to everyone trying to get their foot in the door in whatever field they are in. Thank you and congratulations, Laura!

Raquel

SECTION EDITOR



Raquel Billiones

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Again, I feel pleased and proud of not only what we accomplished but also about how we just might have helped a prospective medical writer take that next career step or helped a company find new talent.

By the time you are reading this, the IF team will be preparing for the Spring 2018 event in Barcelona. Beatrix Doerr stepped down from the chair position of the IF team at the Birmingham event, and I am honoured to succeed her. Please feel free to contact me about the IF, and I look forward to our next event in Barcelona!

Derek Ho

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The second EMWA Live Internship Forum

The birth of the EMWA Internship Forum (IF) took place at the Autumn 2015 conference. It was here that Danae Rokanas and I independently approached the Executive Committee with the idea of an internship scheme that would match prospective medical writers with companies willing to provide them with training and mentorship. Beatrix Doerr agreed to lead us in our endeavour, and the core team was in place by early 2016. A few short months later, we had our first *Live IF* at the Spring 2016 conference in Munich.

We were very pleased with the response to the first IF and felt proud of what we accomplished in such a short time. Regardless of this success, we soon got to work thinking about how the IF could be improved and what we could have done differently.

Two issues were almost immediately evident at the Munich event – space and time. As this was the first *Live IF* and nobody knew what kind of response we would have, we erred on the side of caution and arranged for a total time of 1.5 hours in a small, open-space area reserved for the event.

The interest in the Munich event exceeded our capacity, so we planned accordingly for the Spring 2017 IF in Birmingham. This time, we arranged for our own room, increased the total time of the event (5 hours) and increased the amount of time allocated for the informal and pre-arranged meetings. In addition, Raquel Billiones and Phil Leventhal each gave opening talks, Jackie Johnson and Evguenia Alechine provided career-coaching services, and Peter Llewellyn answered any questions on the world of medical communications. James Pritchett was present to discuss the MSc Science Communication programme at Manchester Metropolitan University.

Like in Munich, it was difficult to predict what kind of response we would have in Birmingham. For me at least, my fears were immediately assuaged when I realised that it was standing room only for the opening lectures. Our career coaches were in meetings non-stop throughout the entire event, and there were lively discussions between applicants and companies throughout the day.



Derek Ho

Shifting your thinking – the first step to getting hired

If you are reading this, you are already headed for success. Your commitment to your education and career goals make you a prime candidate to land an internship in the industry of your choice. That is, if you are willing to do the work. Getting your foot in the door rarely happens by chance. In my experience it required countless hours of preparation and pushing myself to new limits. Ultimately, not only did I land an internship in the pharmaceutical industry, but I also learned a lot along the way.

Lesson 1: Find value in yourself

The truth is that people will not believe in you unless you believe in yourself. To do that, you need to know exactly what it is that you bring to the table. More importantly, you have to believe it.

It's easy to think of yourself as "just a student." I know I did. I often asked myself, *what could I possibly have to offer one of the world's largest pharmaceutical companies?* I wasn't a specialist in any particular field. (In fact, I had changed career paths from psychology to health economics and policy.) I had recently moved to Switzerland to pursue my MA and didn't have any connections in the industry. Moreover, despite being educated, I knew I wasn't a genius. In a sense, I was creating roadblocks for myself by focusing on the things I didn't have. It wasn't until I thought about and believed in my strengths that I saw a clearer path to being hired.

While I may not be a specialist, I have a broad understanding of relevant fields that enables me to look at projects and challenges from various perspectives. Though I didn't have an established network, I certainly wasn't afraid to go out and build one. And even if I will never be a genius, I am committed to learning whatever I do not understand.

We all have something to offer. Some are smarter, some are more qualified, but it isn't until we realise who we are that we can convince others to invest in us.

Lesson 2: Networking is not the enemy

At first, I thought of networking as trying to get hired on the spot. I convinced myself that if I was charming enough, other people would immediately want me on their team. I now know this is simply unrealistic.

After failing to make connections at my first networking event, I knew I had to change my strategy. I stopped looking at networking as a means to find a job and began thinking of it as a



Laura Rodriguez

way to learn from other people. At my next event, I focused more on asking questions and listening to others' experiences. Surprisingly, the conversations were not always work related.

What I learned was that connecting with professionals just means being human. We do not go to networking events to be solicited by others in the same way that we do not answer the 5pm telemarketing phone calls asking if we want to switch our internet provider. Rather, people go to networking events to meet other interesting people and have a good time.

With the help of my new attitude, I walked out of my next event triumphantly. I had met many incredible individuals who not only gave me real insight into the pharmaceutical industry but also wanted to see me succeed. In fact, a few went as far as to recommend me for positions or gave me invaluable tips on how to get hired.

Lesson 3: There is power in rejection

I absolutely blew my first interview. Even worse, I beat myself up about it afterwards by obsessing over what I had done wrong. However, mistakes are more than just mistakes – they are opportunities to learn. I now knew what not to do and concentrated on preparing myself for the next interview. This process of trial and error lasted a few months, and with every rejection, I actively improved. That meant thinking

critically about my responses, writing different versions of my CV, and even signing up for Coursera and the Regulatory Affairs Professionals Society courses to fill my knowledge gaps. This experience both empowered me as an applicant and eventually got me where I am today.

Lesson 4: Sometimes it's just bureaucracy

Along with facing the typical challenges of finding an internship, I had the added pressure of living in a country with strict non-EU work permit regulations. Between cleverly worded laws and permit quotas, finding a job as a non-EU national is very difficult. So much so that many of my talented colleagues are either leaving to pursue opportunities elsewhere in the world or remain unemployed.

Yet many countries have established traineeship agreements that allow graduates to obtain positions internationally. Unfortunately, not all employers know about these agreements and do not consider non-EU applicants because of the challenges associated with employing them. Specifically, businesses may not be able to wait the 3 or more months' processing time for a non-EU work permit or take the risk of having the permit denied.

If you are facing a similar situation, prepare yourself. Take the time to read all relevant legislation, speak with the authorities directly regarding your possibilities, apply early, and discuss realistic timelines with employers. It will not be easy, but it is not impossible.

In the end, things will just work out. Not because you are lucky but because you were determined to make them happen. Good luck!

Laura Rodriguez

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In the Bookstores



How to Write and Publish a Scientific Paper, Eighth Edition

By Barbara Gastel and Robert A. Day;

March 02, 2017.

ISBN: 978-1316640432 (paperback).

24.99 GBP. 344 pages.

A research paper is often the culmination of years' worth of data and experiments, successes and failures, doubts and triumphs, as well as a balancing act between many different opinions from different authors. Writing one can be a daunting task, especially for beginners. Even though most manuscripts are structured in the introduction, methods, results, and discussion format (IMRAD format), jargon and genre norms can confuse first-time writers. And in a world where a single journal (*PLOS ONE*) publishes 80 scientific papers daily, the inexperienced researcher – perhaps writing in their second or third language – may have trouble sorting out the good examples from the bad. Unfortunately, there is a sea of bad examples so immense that it may unmoor even the experienced writer, sending them adrift in the waters of nonsense. The eighth edition of *How to Write and Publish a Scientific Paper* by Barbara Gastel and Robert A. Day is the life raft meant to save the scientific writer from these unsavoury waters and deliver them safely to the shores of clarity.

How to Write and Publish a Scientific Paper begins with a preface, after which Gastel and Day offer a warning: This book contains jokes and humour. These, write Gastel and Day, may confuse some non-native readers. Indeed, the first joke appears in the first sentence of the preface: “Good scientific writing is not a matter of life and death; it is much more serious than that.” And the first cartoon appears only 13 pages into the main body. English being my first language, I welcomed the humour and found most of it to be clear and understandable. The quips and witticisms were easy to distinguish and enlivened what would have otherwise been a dry read. But

The eighth edition of *How to Write and Publish a Scientific Paper* by Barbara Gastel and Robert A. Day is the life raft meant to save the scientific writer from ... unsavoury waters and deliver them safely to the shores of clarity.

I also understand the warning. For instance, there is a small section on scientific style in this book that includes *The Ten Commandments of Good Writing*. While filled with clear jokes about grammatical mistakes, this passage also contains outdated style advice, which made it unclear whether it was written earnestly or sarcastically.

The main body of *How to Write and Publish a Scientific Paper* is 296 pages long and comprises eight parts, divided into 42 chapters, and four appendices. In Part I, Gastel and Day begin with the basics: what a scientific paper is, the history of scientific writing, the development of the IMRAD format, a discussion of ethics, and factors to consider when choosing where to submit a manuscript. Parts II and III are instruction on how to write a scientific paper. In only 72 pages, Gastel and Day teach how to write the title, the abstract, the acknowledgments, the references, and all the IMRAD sections in between. Because this book is intended to be a guide to writing research papers of all scientific disciplines, no specifics are provided for any disciplines, leaving these parts a bit general. Part IV contains useful information often missed by those giving advice on scientific writing. That is, information about submission, peer reviews, reviewer responses, proofs, and publication.

This ends the first half of the book (and the guide to writing a scientific paper); the remaining half (other than the aforementioned section on scientific style) contains useful information beyond the scope of the title. This left me to wonder (about three-quarters of the way through) if future editions should include the subtitle *A Basic Guide to Anything You'll Need to Write in Academia*.

Writing publications other than research papers is covered in Parts V and VI. Brief chapters (about 5 pages each) provide guidance for presenting research orally,

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making posters, and writing reviews, editorials, books, book reviews, and conference reports. Part VII focuses on scientific style and gives advice on aspects of proper English such as avoiding jargon, using abbreviations, and writing science for a community of non-native English speakers. The main body concludes with odds and ends of scientific writing (Part VIII). These include writing theses, grant proposals, cover letters, letters of recommendation, and peer reviews, as well as a section about editing your own work that gives the great advice, “Read your draft aloud. In doing so, you may notice more easily where words are missing or wording is awkward.” Finally, the four appendices cover journal abbreviations, words and expressions to avoid, SI prefix abbreviations, and helpful websites.

Overall, *How to Write and Publish a Scientific Paper* is a very good guide for novice writers. Advanced writers may find the cursory chapters on topics other than scientific papers helpful. I would recommend this book to students, beginners, regulatory writers transitioning into medical communications, and anyone else new to writing academic science.

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Supporting post-submission interactions with health authorities

Medical writers are often involved in the preparation of submission documents such as clinical overviews and clinical summaries. The submission of the application (or, in the case of drugs already approved, a variation or supplement) is an important company milestone, but there is still plenty of work to do. After validation of the submission, the agency reviews the documentation, and a process of back-and-forth begins in which positions are negotiated and concessions may be made.

The details of this post-submission interaction vary according to the type of application and the agency. The European Medicines Agency has well-defined timelines, including so-called clock stops. This agency also usually provides all its questions at the end of the review procedure as part of an assessment report. In contrast, the US Food and Drug Administration is less bound by a pre-specified schedule and may also ask questions during the review procedure. But regardless of the details, the general approach is the same: a list of questions (sometimes called a Request for Supplementary Information) is issued, and the company prepares its responses. Questions can concern any aspect of the submission and may range from fairly simple ones, for example a request to provide a certificate of analysis, to complex ones, such as a fundamental challenge of some aspect of the interpretation of the results. Once the responses have been prepared, they are submitted to the agency for review. More than one round of questions may be needed to reach the end of this process, at which point the agency either approves the application, usually with certain conditions, or rejects it (or the company withdraws its application). For our colleagues more familiar with medical communications and submission of articles, this process can be considered as analogous to peer-review, in which responses to the comments from the peer reviewers are prepared.

Support from medical writers

The response-to-questions document is a central part of the post-submission interaction with the health authorities. For trivial questions (for example, the request to provide a certificate of analysis), little medical writing support may be



required. For more complex issues, though, the medical writer may be able to offer valuable assistance for a number of reasons. First, the medical writer will likely have been closely involved in the preparation of the initial submission and so be familiar with the details of the project. If the list of questions is extensive, skills and know-how of medical writers, such as the ability to manage and oversee complex projects, coordinate input from a variety of sources, and ensure consistency, can be valuable to ensure high-quality responses. The process often requires working to tight deadlines, something that medical writers will be used to. Finally, the tone of the responses also needs careful consideration. The company should sound confident and sure of its position without being dismissive of the reviewers' comments and questions. The language expertise of medical writers can also therefore be important.

Practicalities of response preparation

Before the Request for Supplementary Information arrives, it may be helpful to put together a response team whose members are able to dedicate sufficient time to the responses. The company may also have already made a critical assessment of the application, identified weak areas where questions are likely to be asked, and decided on a high-level strategy for response should these issues be raised during review. Preliminary assessment reports may also be sent to the company, and these can provide some indication of the thinking of the agency reviewers.

Once the actual final Request for Supplementary Information is available, the overall strategy should be finalised as soon as possible. The questions are not always clear and unambiguous and should always be interpreted in the context of the full assessment report, which may provide further clues about the concerns of the reviewers in case of doubt.

When the list of questions is extensive and the timelines are short, it may be helpful to classify the questions according to their level of complexity. Drafting of the response to the "easy" questions can begin straight away in a staggered approach to avoid a log-jam at the end of the process. It is also important to identify questions that may require additional statistical outputs to be produced as this may well be a rate-limiting step.

Final thoughts...

Preparation of responses to Requests for Supplementary Information can be stressful, but it is also rewarding. Preparation of the initial submission is only the start, and the medical writer will likely have worked hard within a team. Involvement in the post-submission process can give the writer the satisfaction of seeing the job through. It can also serve as feedback on how the original submission documents were prepared and provide some enlightenment on what goes through a reviewer's mind. All this will deepen the medical writer's knowledge of the approval process and help make him or her a more complete writer.

Medical Communications

SECTION EDITOR



Lisa Chamberlain James

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Editorial

Dear all,

In this issue, Rossella Ferrari tackles the elephant in the room – how do medical writers manage to find time for their continuing professional development whilst still keeping their head above water with their ongoing project work?

We all know that it is crucial to keep current with regulations and guidelines, and of course we come to EMWA meetings, take the workshops, and attend EMWA webinars

to keep our writing sharp and up to scratch. But what about our disease and therapy area knowledge?

Writers lucky enough to work on a suite of documents or in one area for a long period of time have the relative luxury of seeing their knowledge grow and deepen over time and can focus their attention on one topic. However, far more often we have to swap and change between vastly different disease and therapy areas with alarming speed.

So how do communications writers in

particular stay on top of their game? In this issue, Rossella explains the common problems faced by MedComms writers trying to keep their continuous professional development up to date, and importantly, she shares some fantastic tips and tricks for helping us all to stay sane whilst juggling far too many different disease areas.

These days, I think any steps towards sanity are more than welcome!

Bestest,
Lisa

How to keep up-to-date if you are a MedComms writer

One of the most attractive features of the MedComms area is the variety of topics for writers to cover. However, it is also a challenge to cover many different new therapeutic areas or fields, particularly when we may already be overloaded with writing tasks and pressing time schedules. For example, one week we may be writing a brochure about a new antihypertensive to address a competitor product, the next month we might be focusing on a manuscript about a new phase III trial in oncology; meanwhile an introductory narrative review for a monograph of a new drug for rheumatoid arthritis may be requested by a company that is entering the therapeutic area for the first time. Very often, writing projects arrive in a cluttered sequence.

As with other areas of medical writing, MedComms writers must constantly update and refine their skills and knowledge, and this continuous professional development (CPD) is vital.

This article will outline the ongoing CPD needs for MedComms writers, suggest solutions, and evaluate the opportunities for MedComms writers to specialise by therapeutic area(s).

Definition of the problem

CPD in MedComms encompasses different aspects: we must make sure our background knowledge of the latest clinical and scientific developments is current, our mastery of the latest communication techniques (methods to address the different types of texts) is up to date, and our

ability to fine-tune text in accordance with the desired communication objectives and supporting data is honed.

For each kind of CPD requirement, MedComms writers may choose from various specialised sources. For example, keeping up to date with medical literature is crucial, since it is the basis of every kind of text. Monitoring of changes in legal and ethical issues usually requires less frequent checking for MedComms writers, whereas refresher courses to fine-tune English writing skills may be needed more often, depending on the writer's native language.

Updating medical literature

Although the mastery of different therapeutic/clinical areas increases the amount of time the writer spends working in the area, keeping up to date with the medical literature is challenging because of the huge and increasing number of publications produced per year.¹

The CPD requirement for MedComms writers concerning medical literature is substantially different from that of primary care/specialist physicians: While physicians need to check the literature frequently (daily/weekly/monthly), we need a more top-level overview of a medical field, and so less frequent checks of the literature may be appropriate. Consequently, the tools we use may be different and different criteria will be applied in choosing the literature sources. For example, referring to a series of RSS feeds may not be suitable for MedComms writers

when the task requires a more in-depth knowledge; in this case, the source used for CPD should offer more comprehensive and in-depth information (e.g. a summary of the latest clinical data). However, RSS feeds may be perfectly acceptable sources of information and useful for the latest update, for example, of a manuscript just before submission. Whatever source is used, it is essential that it is a trustworthy source of literature to ensure the reliability of manuscripts and the value of any quotes used.

In terms of medical literature for MedComms, CPD entails:

- Gathering and assimilating the most current knowledge and clinical data of a medical field (one of the most challenging tasks for a MedComms writer);
- Increasing our “competence” in a specified therapeutic area, especially when the area may be vast and ever-increasing;
- Organising and shaping the knowledge collected to focus on the messaging required.

Keeping abreast of *every* medical field continuously and appropriately is not realistically feasible,² and so as MedComms writers, we must be able to critically appraise the available information to orient ourselves among the huge amount of peer-reviewed publications available. In this way, “pre-filtered” sources of literature such as reviews can be essential in summarising a large amount of clinical data and to help answer clinical questions,³ although a recent study has highlighted that systematic reviews reduce, but



do not eliminate, the scatter (or “spread”) of published clinical data across various journals.

Significant differences in this scatter were found between the World Health Organization’s nine diseases with the highest burden.^{4,5} For example, in otolaryngology, randomised trials and systematic reviews have a minimal scatter (i.e. they are not spread over many different

journals) whereas in neurology they have a huge scatter. The increasing number of new journals augments the complexity of this pattern and the corresponding challenge for MedComms writers in CPD.⁵

Other sources of summarised clinical data are guidelines. These can be based on observational studies or randomised clinical trials, although

only a few guidelines still comply with the Guidance for Developers of Health Research Reporting Guidelines.⁶ However, clinical guidelines can be invaluable because they represent a reviewed and agreed update of the latest thinking in a therapeutic area.

Having established the therapeutic area of interest, what MedComms writers need most are systems to enable them to keep up to date with changes in the literature quickly and effectively.

Table 1. Methods of finding literature updates for MedComms writers

Alert systems	<ul style="list-style-type: none"> ● Tables of contents (www.journaltoctoc.hw.ac.uk) for several medical peer-reviewed journals such as: <i>BMJ</i>, <i>NEMJ</i>, <i>JAMA</i>, <i>PLoS One</i>, <i>Oncobiology</i>, and <i>Targets</i> ● Open access publishers (i.e. BioMedCentral) with article alerts based on selection of the preferred journals ● Email alerts from PubMed for selected journals or authors (https://www.nlm.nih.gov/bsd/viewlet/myncbi/jourup/index.html).
Congresses	<ul style="list-style-type: none"> ● free congresses attendance (when possible) ● key reports from congresses
Courses	<ul style="list-style-type: none"> ● 1-day CME courses
Seminars	<ul style="list-style-type: none"> ● organised by universities, hospitals or recognised institutes
Reviews in journals	<p>Open access international journals, such as:</p> <ul style="list-style-type: none"> ● <i>International Journal of Medical Reviews</i> (http://journals.bmsu.ac.ir/ijmr/index.php/ijmr) ● <i>Medical & Clinical Reviews</i> (https://medical-clinical-reviews.imedpub.com) ● <i>International Journal of Medical Research and Review</i> (http://medresearch.in/index.php/IJMRR/) ● <i>Annual Review of Medicine</i> (http://www.annualreviews.org/journal/med). <p>Non open access review articles, in journals such as:</p> <ul style="list-style-type: none"> ● <i>The New England Journal of Medicine</i> ● <i>The BMJ</i>

Literature updating systems

Any updating system should be based on a specific therapeutic area; it should be effective, easy to access and use, not time-consuming, and, if possible, free of charge. Table 1 shows some methods of finding medical literature updates.

The list in Table 1, although far from being exhaustive, provides some examples of literature updating systems. Regular surfing of the web sites suggested may be considered a good starting point. Nevertheless, the choice of the updating system also depends on the frequency of our searches.

Alert systems, as well as webinars, webcasts, RSS feeds, blogs, miniblogs, and some social networking sites, can be specialised for specific medical fields.⁷ Selected over time, they may represent resources of fast updates, and these often are the most popular systems for physicians. However, surveys highlight that alerting services are not always satisfactory or judged positively in terms of content validity and application of evidence-based medicine to clinical practice.⁸ When feasible, attending congresses/courses/seminars and reading review journals are more suitable and reliable sources of

CPD for MedComms writers. We should remember that how often the searches are done and how often we attend congresses, meetings, etc. are crucial factors in the success of the literature and knowledge update method.

Specialisation by therapeutic area(s)

MedComms writers usually have many subjects to monitor, whereas physicians are often specialised and this limits the impact of increasing information overload, even if there are obvious limitations of this approach for clinical purposes.⁵

Although keeping up-to-date with literature in only a specialised area is easier than trying to keep up to date across many therapeutic areas, it is still challenging. Specialisation requires a major competence in a specific area and a major command of the vocabulary of the field. A specialised MedComms writer has a much easier task in terms of CPD, but also has a limited variety of topics in which he/she is knowledgeable, and therefore possibly a more restricted number of work opportunities.

Updating communication techniques

As already discussed, literature updating is not the only CPD requirement for MedComms writers, although it represents a substantial part of it. In terms of style, we have to monitor the evolution and changes in academic jargon. One of the best ways to deal with this issue is to read relevant publications from selected sources as often as possible. The *Journal of English for Academic Purposes* and the “Academic Phrasebank” from Manchester University (<http://www.phrasebank.manchester.ac.uk>) are two examples of suitable resources for writing

articles for peer-reviewed journals.

Grammar and style are other essential components of our CPD duties as MedComms writers because they constitute an important tool of communication fine-tuning. To help with this, many sources are available on academic English web sites, and there are several EMWA seminars available, which have the advantage of being specific to the medical field.

Conclusions

There is no doubt that CPD is an essential part of a MedComms writer’s professional life. To accomplish this, we face, among other numerous challenges, an increasing amount of knowledge needed to keep up to date with clinical developments and evolving communication techniques. This must be managed whilst dealing with a busy succession of writing projects.

The task of CPD is made easier by using effective literature updating systems, and the specialisation in a particular therapeutic area may be an option for some MedComms writers.

However, for a MedComms writer, the greatest challenge is to find a balance between the number of projects that can be accepted and the level of competence in the therapeutic/medical areas involved in the projects. This balance can be achieved with dedication to our own CPD over time.

References

1. Larsen PO, von Ins M. The rate of growth in scientific publication and the decline in coverage provided by Science Citation Index. *Scientometrics* 2010;84:575–603.
2. Garba S, Ahmed A, Mai A et al. Proliferations of scientific medical journals: a burden or a blessing. *Oman Med J* 2010; 25:311–4.

3. Druss BG, Marcus SC. Growth and decentralization of the medical literature: implication for evidence-based medicine. *J Med Libr Assoc* 2005;93:499–501.
4. Gehanno JF, Ladner J, Rollin L et al. How are the different specialties represented on the major journals in general medicine? *BMC Med Inform Decis Mak* 2011;11:3.
5. Hoffmann T, Erueti C, Thorning S, Glasziou P. The scatter of research: cross sectional comparison of randomized trials and systematic reviews across specialties. *BMJ* 2012;344:e3223.
6. Wang X, Chen Y, Yang N et al. Methodology and reporting quality of reporting guidelines: systematic review. *BMC Med Res Methodol* 2015;15:74.
7. Cullis J, Webster AC. How to get the most from the medical literature: keeping up to date in nephrology. *Nephrology (Carlton)* 2010;15:269–76.
8. Strayer SM, Shaughnessy AF, Yew KS, Stephens MB, Slawson DC. Updating clinical knowledge: an evaluation of current information alerting services. *Int J Med Info* 2010;79:824–31.

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The Webscout

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Observational studies

Observational studies are better than their reputation. They have their place in the continuum of clinical research. The following recommended reading will give you an overview of the types of observational studies and their role.

Song and Chung have published a review on two types of observational studies: cohort studies and case-control studies. They highlight the role of these studies in research and discuss methodological issues. In cohort studies, a population with defined characteristics is followed for the occurrence of an outcome of interest. Such studies can be conducted prospectively or retrospectively. The concept of case-control studies is to select patients with a defined disease (case) and subjects without the defined disease (control), and to compare their characteristics to identify prognostic factors for the disease. You can find the review by Song and Chung at www.ncbi.nlm.nih.gov/pmc/articles/PMC2998589.

C.J. Mann has also published a review on observational study designs. In addition to describing cohort and case-control studies, the article also reviews the advantages and disadvantages of cross-sectional studies. You can read the full article at <http://emj.bmj.com/content/20/1/54>. The main purpose of cross-sectional studies is to analyse prevalence at a given time point. However, such studies only measure simple associations and cannot be used to differentiate the effect from the cause.

Randomised controlled studies are of course considered the gold standard in clinical research due to the control for bias and the high validity they offer. So why should you use observational studies? Mariani and Pêgo-Fernandes have summarised their thoughts on the importance of observational studies in an editorial, which you can find here: <https://tinyurl.com/mariani-pego>. The great advantage of observational studies is that they are far closer to clinical practice than a randomised controlled trial.

Sometimes they might even be more suitable than randomised controlled trials. This is often the case when it comes to investigating surgical interventions. Concato et al. have systematically analysed the validity of observational studies in comparison to randomised controlled studies. They conclude that observational studies, if well-designed, do not overestimate effects. The results of observational studies and randomised trials were quite similar for every clinical topic examined, and observational studies were less prone to heterogeneity. According to the authors, this might in part be because, in observational studies, patients are treated according to their individual needs. You can find the full article here: <https://tinyurl.com/Concato-NEJM>.

Although observational studies may be better than their reputation, you still need to be careful when interpreting the results. An "Open Learning Textbook" on biostatistics published by University of Florida Health (<https://tinyurl.com/causation-and-observational>) shows why this is so important. In an observational study, you are much more restricted in your possibilities to control for confounding variables than you are in the conduct of a randomised controlled trial.

This means that you cannot be sure whether an observed outcome is the consequence of your method or treatment or whether another factor has confounded the results. Of course, this can happen in randomised controlled trials as well, but you have more options to control for confounders.

The peer-reviewed journal *Observational Studies* (<http://obsstudies.org>) is a resource on all aspects of observational studies. The journal aims to cover study protocols, methodological aspects, software, descriptions of and access to data sets, and data analyses. An interesting piece I found here is a reprint of an article from 1965 that was authored by William Cochran, a prominent statistician deeply involved in the statistics of observational studies. The reprint is accompanied by comments from leading current researchers in observational studies. You can read the article here: http://obsstudies.org/files/cochran_and_comments.pdf. Cochran saw the potential of observational studies to establish causal relationships when controlled trials are not feasible. But he also urged caution in the interpretation of results: "A claim of proof of cause and effect must carry with it an explanation of the mechanism by which the effect is produced."

Inadequate interpretation and reporting of results from observational studies may have contributed to their bad reputation. To ensure adequate reporting of the results of an observational study, you should follow the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement: www.strobe-statement.org. Similar to the CONSORT statement, which applies to randomised controlled studies, the STROBE statement gives you a checklist of items that you should include when you write a manuscript on the results of an observational study.

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



Teaching Medical Writing

Universities should offer medical writing courses at the undergraduate level



Only one university in the USA offers an undergraduate degree programme in medical writing. Worldwide, fewer than 10 institutions offer advanced degrees (Table 1). Over the past 14 years, I have read and edited many research papers, grant applications, and other materials written by graduate students and established professionals. In many cases, there was significant room for improvement, not only in basic grammar and mechanics, but also in clarity and appropriate diction for the intended audience.

Scientists and health care professionals lack adequate writing skills

Part of the problem stems from lack of exposure to life science-specific writing scenarios at an early stage. Smith et al. point out that “when faced with a particularly challenging and unfamiliar rhetorical task, writers who seem in other contexts to have mastered writing and critical thinking skills as commonly defined will often exhibit basic errors in them”.¹ Moss echoes this concern: “Very few health care professionals are taught how to write”.²

It is in students’ best interests to begin learning about, and practising, medical writing at the undergraduate level. This need is not unique to the USA; in their book, *Healthcare Writing*, Canadian university professors Arntfield and Johnson write:

The university and college curricula required to prepare one for a career in medicine at any level – physician, nurse, technician, or other type of clinical practitioner – seldom make space for advanced course work in commu-

*nications. Seldom have they sought, historically, to assist students in developing nuances of written communication for professional audiences before they make their forays into the care-delivery environment where the stakes are elevated.*³

Tseng and Guo write of the situation in Taiwan:

*... many medical professionals whose first language is not English need to learn academic writing in English because it is the dominant language in academic communications. At most universities in Taiwan, however, academic writing is not included in the undergraduate curriculum, and therefore most of the medical professionals began to learn academic writing after starting their careers.*⁴

A pilot programme for undergraduate medical writing

I developed an online medical writing course at Miami University (Oxford, Ohio, USA) and offered two sections during the 2016–17 academic year. Anticipating diverse student needs and interests, I selected two textbooks:

1. *Writing in the Sciences* by Penrose and Katz, featuring content applicable to all students; and
2. *Writing in the Health Professions* by Heifferon, featuring content applicable to nursing and, to a lesser extent, pre-medical students. The book was included in the course upon advice from the Faculty of Nursing. It was published in 2005, however, and while the basic writing

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concepts are sound, the presentation is obsolete.

Online writing courses are equally, if not more, effective in terms of undergraduate student outcomes.^{5–7} An online course designed with opportunities for interaction among students and the instructor allows students to practise articulating their thoughts through writing and exchanging ideas in a less formal setting while working on formal assignments.

The initial course, an 8-week session, began in October 2016 with 16 nursing, zoology, biology, and pre-medical students. My challenge was creating relevant content for all students, and I presented the course materials in the form of five modules:

1. Introduction: identifying unique medical writing genres with sample readings;
2. Medical records and reports: entering information into patient records and preparing documents such as clinical trial reports, morbidity and mortality reports, and medical error reports;
3. Effective design: formatting research papers for publication, developing educational content for colleagues, and designing patient education materials;
4. Scientific reports and proposals: preparing funding applications, writing progress reports, and collaborating with others to write scientific papers; and

Table 1. Medical writing programmes at universities worldwide

Institution	Location	Level	Credential
Kent University	Canterbury, UK	Graduate	MA in medical humanities
Manchester Metropolitan University	Manchester, UK	Graduate	MSc in science communication
Medical University of Innsbruck	Innsbruck, Austria	Graduate	MSc in medical writing
University of California	San Diego, CA, USA	Graduate	Postgraduate certificate in medical writing
University of Chicago	Chicago, IL, USA	Graduate	Postgraduate certificate in medical writing
University of the Sciences	Philadelphia, PA, USA	Graduate	Master’s in biomedical writing
University of Worcester	St. John’s, UK	Graduate	Postgraduate certificate in medical writing
Carnegie Mellon University	Pittsburgh, PA, USA	Undergraduate	BSc in professional writing

5. Employment, graduate school, and medical school applications.

I used the writing assignments such as clinical narratives and scientific report critiques to emphasise the importance of rhetorical analysis and audience awareness in life science settings. The final examination was a white paper assignment (a concise evaluation of a selected topic). It was assigned at the beginning of the term to allow students adequate time to research, prepare, write, and revise. My goal was for them to apply the writing and design principles they learned during our 8-week session. Students were permitted to select their own topics, such as evaluating alternative therapies and exploring a new treatment for opioid addiction.

Students in online courses are accustomed to participating in social media, so they were comfortable with the prospect of using the course discussion board. This was especially effective for exercises such as charting; those who had never seen a medical chart learned a great deal from the experienced students about what should be entered, by whom, and why. Students also engaged in lively discussions regarding ethical situations, health care advertising, badly written prose (their science textbooks were often excellent source material), specific aims for grant applications, and other topics.

The second course lasted an entire semester (January to May 2017), enabling 20 students to engage in additional discussions and develop written assignments. The nursing and pre-medical students found the extra time to learn about charting and medical documentation especially helpful.

Results and evaluation

The student population ranged from “traditional” full-time students to full-time health care professionals, some with over 20 years of experience. Students had the option to complete course evaluations; while the typical response rate varies from 8% to 35%, 53% of the first-course students and 72% of the second-course students completed evaluations.

All respondents in the first course, and all but one in the second course, agreed or strongly agreed with the following statements:

- Course assignments and activities advanced my analytical and/or creative abilities.
- The course was intellectually challenging.
- I strengthened my reading and/or writing ability over the course of this class.

- My appreciation for this topic has increased as a result of this course.

One nursing student in the second course expressed frustration with being asked to write clinical narratives. She had been advised by her faculty to take the course in her second year, before she had gained any clinical experience. I will re-evaluate the assignment.

The students agreed that the textbooks were not especially helpful because they were outdated. Of the individual written assignments, they most enjoyed designing and writing patient education brochures. This required awareness of both text and visuals when communicating with diverse readers, and they appreciated the challenge of developing effective materials for a lay audience while being mindful of international and multicultural sensitivity.

Future direction

The most important change I will implement is requiring two different, updated textbooks:

1. *Healthcare Writing: A Practical Guide to Professional Success* by Arntfield and Johnston. This reasonably priced and very readable book provides practical advice for a variety of writing situations, including research reports. It is applicable to both clinicians and scientists.
2. *Medical Communication: Defining the Discipline* by Polack and Avtgis. Written by a physician and a communication scientist, this book is oriented toward clinicians and those involved in clinical trials. It will serve as a valuable reference throughout their careers.

The students suggested a peer review session for their final papers. This is an important part of the publication process and would be a good extension of the scientific report critique, providing additional practice in reading and thinking critically. Furthermore, I plan to implement “career track oriented” assignments; for nursing students, for example, this could entail additional practice with medical documentation such as charting. Aspiring scientists, clinician-scientists, and medical writers would likely benefit from practice writing research-oriented documents.

As with other writing classes, “one size fits all” is an unattainable goal, but it is important for students to have adequate instruction and resources to learn what they need to know. At the same time, it is important for students to realise their careers will involve more writing than they may have initially believed.

Conclusion

To obtain research funding, publish manuscripts, and ultimately play a role in advancing medical science, scientists and clinicians must be able to communicate their findings. Furthermore, they must be able to convince people from their own and other disciplines of the importance of their research discoveries. The ability to write well is essential to this process, and the sooner students learn to do so, the greater the benefit. Therefore, any undergraduate institution offering medical, life science, and/or nursing programmes should develop and offer courses in medical writing.

References

1. Smith TG, Ariail J, Richards-Slaughter S, Kerr L. Teaching professional writing in an academic health sciences center: the writing center model at the Medical University of South Carolina. *Teach Learn Med* 2011; 23:298–300.
2. Moss F. Writing is an essential communication skill: let’s start teaching it. *Postgrad Med J* 2015;91:301–2.
3. Arntfield M, Johnston J. *Healthcare writing: a practical guide to professional success*. 1st ed. Peterborough: Broadview Press; 2016.
4. Tseng YC, Guo HR. Teaching academic writing to medical professionals using computer communication media. 2012 International Symposium on Information Technology in Medicine and Education (ITME) 2012;1:58–9.
5. Nguyen T. The effectiveness of online learning: beyond no significant difference and future horizons. *Merlot J Online Learn Teach* 2015;11:309–19.
6. Jaggars S, Xu D. *Online learning in the Virginia community college system*. New York: Columbia University Teachers College; 2010.
7. George PP, Papachristou N, Belisario JM et al. Online eLearning for undergraduates in health professions: A systematic review of the impact on knowledge, skills, attitudes and satisfaction. *J Glob Health* 2014;4:1–17.

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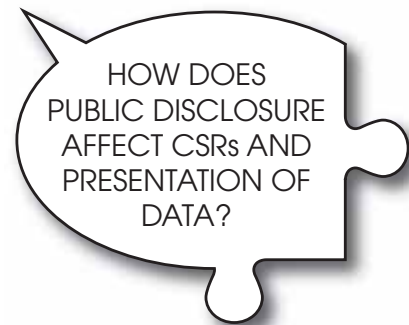
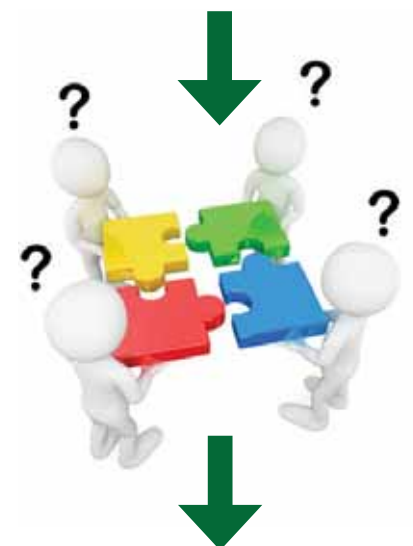
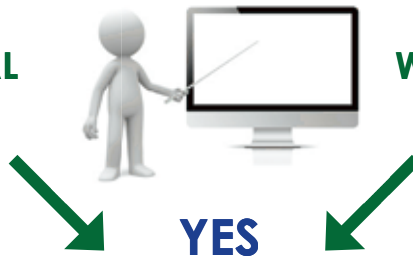
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Good Writing Practice

Syntactic Structure - Inter-sentence

Incrementalism: Sentences



Introduction

Inter-sentence incrementalism is an expansion of information, often secondary, into a sentence rather than a reduction of the information to a clause or phrase and incorporation (sentence combining) into a contiguous sentence. Such incrementalism may be a consequence of the advice to express ideas as a series of short sentences to avoid grammatical mistakes. Although there is wisdom to this advice, such information expansion conveys a non-professional tone and seems tedious and

simplicistic to an expert in the discipline who expects a focused interrelation of thought achievable by sentence combining. Incrementalism is organised into three subsections according to how a reduced syntactic structure is incorporated into a contiguous sentence: coordination; modification; apposition.

Coordination

In the first part of our examination of inter-sentence incrementalism, we look at coordination subdivided into the following syntactically

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reduced structures: independent clause of a compound sentence (Part 1); noun clause (Part 2); noun phrase (Part 3).

Part 1 - Independent clause of a compound sentence

Example: Discussion section: limitation

An MT-like protein was present in this polychaete. However, amino acid analysis is necessary for confirmation.

confirmation.

Revision 1

An MT-like protein was present in this polychaete; however, amino acid analysis is necessary for confirmation.

Revision 2

An MT-like protein was present in this polychaete, but amino acid analysis is necessary for confirmation.

Notes

The rhetorical advantage gained by coordinating two sentences into a compound sentence is information relatedness. In the example, the separateness of the sentences emphasises their individual importance, whereas sentence-combining in the revisions bridges their relatedness.

In the compound sentence of Revision 1, the independent clauses are more visually and cognitively integrated than are the separate sentences in the example. A sentence conveying a contrast may be more effective when transformed into the independent clause of a compound sentence. This transformation, the least dramatic reduction in hierarchical syntax, is from two sentences into a compound sentence separated by either a semicolon or a comma.

In Revision 2, the independent clauses of a comma-separated compound sentence seem more interrelated than in Revision 1, because a

comma is a weaker border marker than a semicolon.

In the Example and Revision 1, *however* is a conjunctive adverb followed by a comma that contrasts information in an independent clause with information in an immediately preceding independent clause. The comma distinguishes the conjunctive adverb from an intra-clause adverb, whereby *however* functions as an adverb modifying a constituent in the clause in which it occurs as in *however exhaustive the purification method, protein purity is not assured*. In this situation, *however* is not followed by a comma.

Part 2 - Noun clause

Example: Introduction section: research importance

The results of the proposed study are important for understanding how joint pressure affects the physiology and pathology of the TMJ. This study will also indicate the effect of mandibular position on mandibular growth.

Revision

*The results of the proposed study are important for understanding how joint pressure affects the physiology and pathology of the TMJ **and how mandibular position affects mandibular growth.***

Notes

There are cues that justify sentence combining. The repetitive *this study* is a cue that the two-sentence example emphasises *the study* at the expense of what was to be accomplished. Coordinating the potential accomplishments as noun clause objects (of the preposition *gerund for understanding*) renders the accomplishments equivalent in importance rather than does the second sentence of the example, which seems as a tag-on (i.e., of lesser importance than the joint pressure).

Part 3 - Noun phrase

Example 1: Materials and Methods section: method

Then, the participants were instructed to perform two instructed practice trials. Afterward, they had 2 minutes' rest. Finally, they performed three test trials.

Revision

The sequence for the participants was two instructed practice trials, 2 minutes' rest, and three test trials.

Notes

The three successive time-focused transitional expressions are just too story-like (i.e., narrative). The repetition of time-focused transitional expressions emphasises the time at the expense of the conceptual components. In addition to the

narrativism of the transition expressions, there is an underlying narrativism caused by the incremental sequence of subjects and actions in the three sentences. In the revision, the sequence of actions (including the first sentence) is expressed as a descriptive coordinated listing rather than incrementalised actions.

A narrative pattern is informal compared to a descriptive format consisting of a thematic topic (instead of an agent) as the subject and the linking verb (instead of an action verb) as the predicate.

Example 2: Introduction section: research problem

Previous studies were based on small sample size. And interviews were delayed ~16 years after term.

Revision

*Previous studies were based on small sample size **and delayed interviews (~16 years after term).***

Notes

The second sentence in the Example does emphasise the *delayed interviews* but at the expense of the *sample size*. That is, it seems the succeeding sentences will concern the *delayed interviews* and not the *sample size*. In contrast, coordination in the revision renders the *sample size* and *delayed interviews* as coordinate causes of the research problem.

The revision involves syntactic reduction of the second sentence into a noun phrase *delayed interviews*, which is coordinated with the object (of a prepositional phrase) *small sample size*. Further syntactic reduction (primarily visual) is accomplished by parenthesis of the adverbial appositive noun phrase *~16 years after term*.

Modification

Another type of sentence incrementalism occurs with modification, which is organised according to a better match between structure and function than a full sentence: noun phrase (Part 4); infinitive phrase (Part 5); prepositional phrase (Part 6); and elliptical adverb clause (Part 7).

Part 4 - Noun phrase

Example: Introduction section, research problem pertinent background

In the dental mesenchyme, Msx-1 is required for induction of syndecan-1 expression by BMP-4 (Ref). BMP-4 is also a downstream target of Msx-1 (Ref).

Revision 1

*In the dental mesenchyme, Msx-1 is required for induction of syndecan-1 expression by BMP-4 (Ref), **which is also a downstream target of Msx-1 (Ref).***

Revision 2

*In the dental mesenchyme, Msx-1 is required for induction of syndecan-1 expression by BMP-4 (Ref), **a downstream target of Msx-1 (Ref).***

Notes

A sentence that describes a noun in a preceding sentence may be better matched to its relative importance when conveyed as a dependent adjective clause. In Revision 1, syntactically reducing the second sentence into an adjective clause and combining the clause with the first sentence to form a complex sentence is not more concise. Both the incremental adjectival description and its reduced adjective clause (Revision 1) contain 8 words. However, further syntactic reduction into an appositive noun phrase, containing just 5 words, maintains the thematic focus on MSX-1.

The adjective clause, somewhat emphasised by its length and end position, is known also as a relative clause, because it is fronted by the relative pronoun *which*.

Part 5 - Infinitive phrase

Example: Introduction section: research objective

A robust delay fault simulation was performed. The purpose of this simulation was to identify robust-testing paths.

Revision

*A robust delay fault simulation was performed **to identify robust-testing paths.***

Notes

The infinitive phrase succinctly conveys an objective, rendering unnecessary the redundant syntactically over-emphasised and incrementalised statement *the purpose of this simulation was*.

Part 6 - Prepositional phrase

Example: Materials and Methods section: method

The resulting homogenate was then centrifuged (5 min, 4°C). Next, the gels were incubated in buffer containing 5 mM CaCl₂.

Revision 1

After the resulting homogenate was centrifuged (5 min, 4°C), the gels were incubated in buffer containing 5 mM CaCl₂.

Revision 2

After homogenate centrifugation (5 min, 4°C), the gels were incubated in buffer containing 5 mM CaCl₂.

Notes

The incrementalism is more rhetorically matched

to laboratory instructions than to a journal article descriptive format of a Materials and Methods section. Such incrementalism is lessened by sentence combining, whereby the first sentence is partially deemphasised as a dependent adverb clause (Revision 1) and further into a prepositional phrase (Revision 2). This further revision is justified by the narrativism and by the superfluous information *the resulting*.

Part 7 - Elliptical Adverb Clause

Example: Discussion section: conclusion

The actual cause for decreased collagen hydroxylation is conjecture. However, the strong correlation between decreased hydroxylation and the degree of hyperglycaemia is consistent with a glucose-mediated effect.

Revision 1

Although the actual cause for decreased collagen hydroxylation is conjecture, the strong correlation between decreased hydroxylation and the degree of hyperglycaemia is consistent with a glucose-mediated effect.

Revision 2

Although conjecture, the strong correlation between decreased hydroxylation and the degree of hyperglycaemia is consistent with a glucose-mediated effect.

Notes

In the example, the second of the two independent clauses merits emphasis. Therefore, the first independent clause is syntactically reduced into an adverbial dependent clause (Revision 1) and further into an elliptical version (Revision 2).

Apposition

The focus in this subsection is on sentences expressing secondary information that could be in apposition to information in a contiguous sentence. The examples are arranged according to the syntactically reduced units: noun phrase (Part 8); and listed noun phrases (Part 9).

Part 8 - Noun phrase

Example: Introduction section, research problem pertinent background

Phoneme detection is designed to test the human ability to understand the different phonemes that constitute the spoken word. By this test, the experimenter pronounces a pseudoword. An example of a pseudoword is shalt. The individual repeats that word to ensure accurate encoding.

Revision

Phoneme detection is designed to test the human ability to understand the different phonemes that



constitute the spoken word. By this test, the experimenter pronounces a pseudoword (e.g., **shalt**). The individual repeats that word to ensure accurate encoding.

Notes

Succinctness is achieved by attenuating an entire sentence into the embeddable appositive *shalt* of a contiguous sentence. This is a prototypic example of syntactic reduction whereby secondary information (an example) is reduced into a noun phrase instead of its incremental over-emphasis as a sentence.

Part 9 - Listed noun phrases

Example 1: Materials and Methods section: method

A sample of 100 pre- and post-treatment patient records were examined from one orthodontic office in Yorba Linda, CA. Patient records consisted of study models, panoramic radiographs, intra- and extra-oral photos, and detailed medical histories.

Revision

From one orthodontic office (in Yorba Linda, CA), examined patient records consisted of study models, panoramic radiographs, intra- and extra-oral photos, and detailed medical histories.

Notes

The passive verb phrase *were examined* of the first sentence is reduced into the past participial phrase *examined* thereby enabling incorporation of the phrasal verb *consisted of* from the second sentence. The cue justifying sentence combining is repetition of the *patient records* in sentence 2.

Example 2: Materials and Methods section: method

Pregnant female Sprague-Dawley rats (Simonsen Inc.) were individually housed (standard cages; 21°C; 12 h light-dark cycle). From the brains of their embryonic day-18 fetuses, nerve cells were prepared.

Revision

Nerve cells were prepared from the brains of embryonic day-18 fetuses of pregnant female rats (**Sprague-Dawley; Simonsen Inc.; individually housed, standard cages; 21°C; 12 h light-dark cycle**).

Notes

The intended focus is the nerve cells. Thus, in the revision, multiple details are appositively listed and parenthesised.

Summary

Focused paragraphs can be written by syntactically reducing sentences into phrases that coordinate, modify, or appose information in a contiguous sentence. Overall, information that is incrementally expressed in sentences can be reduced into pinpoint placement next to pertinent information, thus achieving succinctness and clarity.

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Out on Our Own

Editorial

Greetings, readers.

For freelancers, receiving feedback is an important process for building a mutually productive relationship with a client. Positive feedback serves to encourage and helps develop core strengths, while constructive criticism is educational and facilitates identifying weaknesses and areas to work on. Hence, in absence of a 'boss' or "annual appraisals", it is the client's feedback that is crucial for the professional development of a freelancer. But perhaps you will agree with me when I state that accepting negative feedback with equanimity is indeed difficult. In her article, Michelle Guillemard, the President of the

Australasian Medical Writers Association and an avid blogger on freelancing issues, presents a few tips on preparing well to avoid unfavourable feedback from the client and handling it effectively if it does happen.

While medical writing is considered an established profession in Europe and the USA, there still are many countries in the world where this is not the case, resulting in a dearth of qualified medical writers to assist the pharmaceutical and healthcare industry, regulatory bodies, and academic and research institutions. It certainly is the case in Evguenia Alechine's homeland, Argentina. From finishing her PhD and leaving academia a few years ago to currently being a successful freelancer, Evguenia has come

a long way. In all this, she has also found time to volunteer for EMWA's Internship Forum to help newbies in a career in medical writing. In this issue of the OOOO, Evguenia tells us her story on how her interest in scientific communication developed into a career in medical writing, why she decided to become a freelancer, and how she plans to soon develop medical writing as a profession in South America.

I hope you enjoy these articles. As always, I invite you to send in your contributions to and suggestions for the OOOO section. Last, but not least, my personal thanks to Michelle and Evguenia for sharing their articles with us.

Satyen Shenoy

Preventing negative feedback and learning from complaints

Bill Gates once said, "Your most unhappy customers are your greatest source of learning."

It's not easy to digest, is it? Think about a time when you were given negative feedback, someone complained about your work, or a project didn't go as well as it should have.

It's much easier – and you'll often feel better – to simply dismiss negative feedback as someone else's problem that has nothing to do with you. But this approach could be doing you more harm than good. In the business magazine *Fast Company*, Denis Wilson wrote:

Research shows people that are better at handling negative feedback tend to be more successful – and those that can't are less so. ... "Being able to accept feedback requires a modicum of critical self-awareness", says Mark Murphy, founder of Leadership IQ and author of Hiring for Attitude. "If you are of the belief that you never make mistakes, you probably have a narcissistic personality disorder, and it's going to be really hard to give you feedback. Somebody who has enough self-awareness to recognise they might need feedback, that's the person that's going to say 'Even when I'm on my best game, there's always something I could have done to be better'".¹

Learning from complaints and negative feedback

When you're a freelance writer, it's unlikely a client is going to write you a letter of complaint as such. Still, you may need to deal with negative feedback from time to time. Or, a client may complain about the way a job was managed if a project didn't run as smoothly as you would have hoped.

Sure, we could get defensive and grumpy every time someone doesn't like our work. But, a better approach would be for us to learn from negative feedback and complaints. We can, and should, listen and react – meaning we should aim to understand the complainant's point of view and put steps in place to ensure the same sort of negative feedback doesn't happen again. Like many things in life, a big part of dealing with complaints and negative feedback comes down to mindset. The outcome of any complaint can be influenced by our attitudes and how we choose to handle a situation. Only we can control how a situation or a person makes us feel. And, accepting we have the power to turn a negative into a positive can be a very poignant realisation.

Preventing negative feedback

Obviously, the best way to deal with complaints is to ensure they never happen in the first place. That's clearly easier said than done, but, there are

several very good strategies for preventing negative feedback which will help reduce the risk of client and customer complaints. Being extremely thorough in the pre-planning stages of every project is key.

Here's what I suggest:

- **Spend a lot of time pre-planning and gathering requirements.**² I need to know exactly what I'm doing, how I'm helping the client, and what elements are mandatory to the project.
- **Send samples of your work³ before you agree to go ahead on a project.** I want my clients to know my writing style, what I'm capable of, and what they're in for.
- **Ensure all terms of working together are clearly defined.** Have systems in place for delays, late payments, and emergencies.
- **Refuse work that is too far outside of your comfort zone.** I know my strengths and weaknesses, and if I don't feel I can do a good job, I won't take on a project.
- **Keep in touch during the project.** Recently, I was rewriting an entire website dedicated to radiation therapy. It was 60,000 words – which is pretty much an entire book! Do you think I wanted to send that to my client without showing at least a bit of it to them first? We agreed I would send them a few



pages so they could see how I was progressing. They gave me feedback, which I then applied to the rest of the project. The result? When I sent the first draft of the 60,000-page booklet, I only needed to spend about an hour tidying up some very minor points during the revision process.

- **Document absolutely everything in writing.** Everything you agree to do should be documented via email – and, even if you chat on the phone, summarise the key points in writing so there's no confusion later.
- **Spell everything out.** Leave no stone unturned when it comes to defining requirements, mandatory inclusions, costs, processes, your writing style, and deadlines.

The benefit of doing all these things is not just preventing complaints. These processes also provide a smooth working relationship, ensure you're delivering what the client or customer wants, and give you a good chance of securing ongoing work with the client.

If you do get a complaint or negative feedback

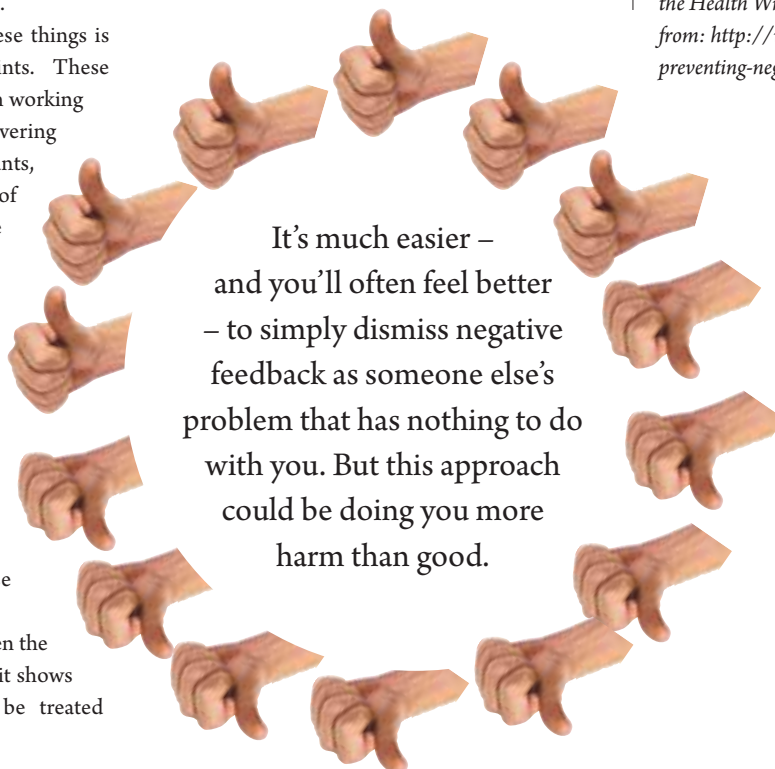
You can still do all those things I mentioned above and get complaints or negative feedback. Unfortunately, this is a part of running a business and even working in general. We can't please everyone all the time.

Remember, if someone has taken the time to tell you they're not happy, it shows they care. All feedback should be treated

seriously and graciously, with clear acknowledgement and a response. After all, if someone is critical of your work and never mentions it, you'll never know there's a problem – and this can be worse.

The other thing is, you're not always in the wrong if someone criticises your writing.⁴ So how *do* you know if feedback is justified or not? Assuming everything is your fault can be just as damaging as assuming nothing is your fault.

Perhaps the answer lies in another powerful quote from Wilson of *Fast Company*: "You do need a degree of resiliency and the ability to filter the junk data from the good data in order to improve."¹



References

1. Wilson D. Thick skin thinking: how to use negative feedback to your advantage at work. *Fast Company* [Internet]. 2012 Oct 26 [cited 2017 Jun 29]. Available from: <https://www.fastcompany.com/3002460/thick-skin-thinking-how-use-negative-feedback-your-advantage-work>.
2. Guillemard M. Gathering requirements before you start writing. *Health Writer Hub* [Internet]. 2015 Nov 03 [cited 2017 Jun 29]. Available from: <http://www.healthwriterhub.com/gathering-requirements-before-you-start-writing/>.
3. Guillemard M. How to build your health writing portfolio. *Health Writer Hub* [Internet]. 2015 Dec 02 [cited 2017 Jun 29]. Available from: <http://www.healthwriterhub.com/how-to-build-your-health-writing-portfolio/>.
4. Lambert R. Learning to handle writing criticism. *Health Writer Hub* [Internet]. 2014 Jul 06 [cited 2017 Jun 29]. Available from: <http://www.healthwriterhub.com/writing-criticism/>.

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Note: A version of this article was previously published as a blog post by Michelle Guillemard on the Health Writer Hub website and is available from: <http://www.healthwriterhub.com/preventing-negative-feedback/>

Somewhere on my own, but never alone: My career path from Argentina to science communication



Since I joined EMWA almost 2 years ago, I have always wanted to tell my story, and after reading the article by Ricardo Wilches,¹ published in the last issue of *Oooo*, I was inspired to share my own career path as being “Oooo” in South America.

Only after I finished my PhD and left academia, I realised how much I enjoy writing (and editing others’ writing), especially about science, health, and medicine. But, it was not before I met Jackie Johnson that I knew medical writing is the career path I want to pursue.

The possibilities of me becoming a medical writer in Argentina were not that much. Most of the people do not know medical writing, while those who do, outsource this task to professionals abroad. Despite having a significant pharma industry and several CROs based in the country, medical writing is quite an unknown field in Argentina.

Therefore, when I started, I had to face some challenges. First, I had to acquire medical writing and scientific editing skills. Since there are no such courses in Argentina, especially not in English, I decided to take two parallel paths: attending the workshops held at EMWA conferences and enrolling in AMWA’s self-study Essential Skills certificate.

Moreover, since I aimed to pursue a career in scientific communications, specifically as a scientific editor, I started looking for training opportunities; albeit without much success. At this point I decided to make an investment in attending my first EMWA conference, in Munich. What happened at and after the conference is hard to describe – from networking with medical writers from all over the world and attending amazing workshops, to joining EMWA’s social media team. Without much awareness, my relationship with EMWA grew into invitations to become a table leader for the Show IT, Share IT session, the Freelance Business Forum, becoming

a section editor for *Medical Writing*, and running a career coaching at the Internship Forum, among other projects.²

In the past two years, I have already attended three conferences and taken at least a dozen workshops, and this allowed me not only to gain new skills, but also to build confidence in my abilities as a science communicator. I consider myself an eternal learner, so taking courses and attending workshops is what I love doing; but, of course, this is not the only way to become proficient in scientific communication.

To be honest, the learning part was quite easy, the difficult part was finding my first clients. At this point, I made the decision to freelance for several international companies before reaching out to individual clients in Argentina. This experience had its pros and cons. On one hand, I received a tough training and gained experience. On the other hand, I started working on an extremely low rate to “compensate” for my lack of experience. However, this experience taught me the kind of work I wanted to do as a freelancer while also allowing me to gain credibility in the eyes of prospective clients. Now, after freelancing for several companies and individual clients, I landed a full-time position as a scientific editor and writer for a company that not only acknowledges my scientific value but is also in line with my personal beliefs.

One of the most amazing things that I experienced in this path was being able to share my knowledge. While I was in academia, I really enjoyed teaching. Now, as a science communicator, I offer training to those who do not have the possibility to travel abroad and attend high-quality workshops. Science communication in Argentina is often hindered by two shortcomings: a lack of proficiency in English and absence of appropriate communication training in the curriculum of science and healthcare professionals. In the light of this reality, I started

offering scientific communication training at private centres, biomedical organisations, and universities – one of my current responsibilities that gives me the utmost joy.

In line with my calling to pursue teaching, I found myself offering career development coaching to PhDs in and outside Argentina. Many current and former scientists are not aware of their value to the scientific communication industry and the career options out there. I feel that it is both my duty and my reward to inform and inspire these highly qualified prospective scientific communicators.

It seems like time has flown since I started on this path. Recently, I also earned my ELS certification from the Board of Editors in the Life Sciences (BELS) after taking the exam in Birmingham right before the last EMWA conference. Not only was I the first Argentinean to join EMWA, but now I’m also the first certified ELS in South America. With all this and my own experience in mind, my next challenge is bringing medical writing to South America, in collaboration with Ricardo Wilches from Colombia.

My goal behind writing this article is to inspire those who might also be “out on their own” in countries outside Europe to explore the medical writing career path, even if this path is a bit bumpy and it takes more time to reach the finish line.

References

1. Wilches R. Becoming a science communicator – in my own words. *Med Writ* 2017;26:78–9.
2. Alechine E. The black tag. *Med Writ* 2017;26:64–5.

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Upcoming issues of **Medical Writing**



December 2017: **Preclinical studies**

This will include articles on designing, analysing, and reporting preclinical studies.

The deadline for feature articles is September 11, 2017.



March 2018: **Vaccines and immunotherapies**

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June 2018: **Public disclosure before editing**

This issue will cover public disclosure and publication of clinical trial results, especially including recommendations and requirements from the European Medicines Agency.

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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.

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If you have ideas for themes or would like to discuss any other issues, please write to mew@emwa.org.



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