

# Medical Writing



## Patient-reported outcomes

### Also in this issue...

- The UK pharmaceutical industry braces for Brexit, be it mild, severe, or doomsday
- Awareness of medical writing profession and its career prospects in India
- Protecting the rights of clinical trial patients through disclosure: The significance of plain language



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

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# Medical Writing

## Patient-reported outcomes

Enabling the patient's voice to be heard in healthcare settings

You are very welcome to this special edition of *Medical Writing* where the focus is on patient-reported outcomes (PROs). This is my second time to act as a guest editor. Once again, in the process of putting the issue together, I was highly impressed by the breadth and level of knowledge possessed by EMWA members. My sincere thanks to everyone who has contributed to this issue in whatever form. It really was a joy to work with you all – as well as being very educational. The end result is that whether you are new to the topic or a seasoned PRO pro(!), there is something for everyone in this issue.

I am very pleased that **Paul Kind**, a founder member and past president of the EuroQoL Group, contributed an article to this issue. His piece notes that there is not a universally agreed understanding of the meaning of health. His article expertly outlines the historical and philosophical milestones that point to the future of modern healthcare.

A nice article to follow Paul's, especially if you are new to the topic of quality of life measures, is **Maria Koltowska-Hägström's** overview. She succinctly outlines the various models and scales that every medical writer should know about. Maria delves even deeper into the topic with her second article exploring the different health-related quality of life (HR-QoL) categories.

Of course, as medical writers we are keen to know what impact PROs can have on us and our work. One such element is considered by **Richard White** in his article that demonstrates the valuable role PROs can play in publication planning. His article contains many useful writing tips and addresses the 'so what?' question that all of us in clinical research have heard at one time or another.

**Cate Talley** and **Shawn McKown** provide a great overview of the issues surrounding translation of PRO measures, a challenge I know from personal experience that researchers can easily underestimate.

We also have a couple of feature articles examining how PROs are being used in real life. From Denmark, **Rikke Havner Alrø**, **Marie-Louise Krogh**, and **Claire Gudex** share their experiences of systematic hospital collection of

PRO data via patient apps. The first results look promising. The apps appear to help staff focus on the individual patient's needs. They can even eliminate hospital visits for elderly patients, as well as improving communication in general. Incidentally, it was Claire along with Maria Koltowska-Hägström who helped me to find the lion's share of contributors for this issue so a special thanks to you both.

In a similar vein to the Danish paper, I also contributed an article that reports on the use of a patient app for total knee arthroplasty patients in clinical trials in the UK and the US. The article also outlines the advantages of electronic PRO collection over paper-based systems.

I was also interested in learning more from the people who develop PROs. Within this issue you can read my short interview with **Professor Matthias Rose**, Medical Director of the Psychosomatic Department at the Charité University Hospital. Professor Rose has an enthusiasm for PROs that is infectious, and the useful knack of explaining the issues to those who do not possess his level of knowledge about PROs.

I was highly impressed by the breadth and level of knowledge possessed by EMWA members.

Of course, not all of this issue focuses on PROs. **David Rogers**, **Ben Rogers**, **Jacob Lewis**, **Jonathan Oliver**, and **Elsa Lewis** tackle the thorny issue of Brexit and the possible scenarios for the UK pharmaceutical industry. **Pinki Rajeev** and **Mittal Makhija** examine awareness levels among over 150 Indian medical writers of their prospects within the industry. **Helen Bridge** and **Thomas Schindler** attempt to close the gap between study design and analysis. In clinical research, we have to be very respectful of the patients taking part in trials. **Rosemary Meister** investigates how plain language can assist in protecting the rights of clinical trial patients.

Once again, my sincere thanks again to all of the contributors (feature articles as well as the regular sections), as well as to Phillip Leventhal, Victoria White, and the *Medical Writing* editorial team for helping to make it happen.

Now go and enjoy this issue of *Medical Writing* on patient-reported outcomes!



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# President's Message

## Dear EMWA Members,

Exciting news from our conference in Warsaw! Besides the excellent conference programme, there were a few updates and initiatives going on "behind the curtains". First of all, I would like to thank our workshop leaders, members of the EMWA Professional Development Committee (EPDC), the Executive Committee, and all volunteers for their great support in planning, organising, and running the conference. We had 95 members attending for the first time (many green lanyards!), more than 40% of the overall number of registrants. We were delighted to welcome these new attendees and hope they enjoyed the conference. Among the 31 workshops run in Warsaw, we had six new ones, and five further workshops are currently under development and will be available soon. There is much work ongoing to broaden the offer of topics for our members. A few writing areas of growing interest have been specifically addressed such as pharmacovigilance, public disclosure, and medical devices. A recent webinar provided insights into veterinary medical writing. Although "vet writers" still represent a minority at EMWA, we are interested in hearing their voice: What are the skills and topics you would like to be trained on? If you are already experienced, would you be interested in volunteering to strengthen this area at EMWA? The EPDC volunteers are always grateful for new ideas and suggestions, as this helps to shape EMWA to the needs of the members.

Besides the educational programme, there are other ways for EMWA to train and update their members, such as expert seminar series and symposia, conference sessions, topic-related discussions and reviews, and collaborations with other professional associations. Based on a suggestion made by one of our experienced members, we are currently establishing a working group of experts on the topic of predatory publishing/journals. This issue needs to be communicated to medical writers and communicators. Training initiatives within EMWA, as well as close collaboration with other professional associations, are needed to raise awareness on this subject. To identify further relevant issues, we have asked our Nick Thompson fellows to explore topics and investigate the potential for training, events, or collaborations, based on their expertise and their perspective as experienced members.

Based on a suggestion made by one of our experienced members, we are currently establishing a working group of experts on the topic of predatory publishing/journals.



At the opening session of the conference in Warsaw, Sam Hamilton and Art Gertel shared an important update:

*CORE Reference, downloaded 14,500+ times, continues to gain traction globally. Public declarations of support from pharmaceutical companies and CROs [clinical research organisations] are a testament to the perceived value of CORE Reference in reporting modern design interventional clinical trials. TransCelerate Biopharma, an alliance of selected prominent pharmaceutical companies, plans to release a CSR [clinical study report] template in Q4 2018. At the November 2018 AMWA Conference in Washington DC, representatives of the TransCelerate CSR template development team advised Art Gertel, strategist for the CORE Reference project, that CORE Reference and ICH E3 were considered pivotal in developing the CSR template.*

EMWA is very proud of being part of this exciting project!

Collaborations like the CORE Reference and the Joint Position Statement are a valuable way

to strengthen EMWA as a reference organisation for professional medical writers and its role in public discussions. Our association was recently invited to contribute to the development of a new outcome reporting standard for clinical trial protocols and reports of completed trials, called the Instrument for reporting Planned Endpoints in Clinical Trials (InsPECT). We have already shared this invitation with our members through the website and social media. Furthermore, EMWA, the American Medical Writers Association, and the International Society for Medical Publication Professionals have recently been contacted by the EQUATOR Network to perform a joint review of the CONSORT guidelines and to spread the word about the EQUATOR Good Reporting tool. There are various other initiatives ongoing "behind the curtains", and I look forward to reporting on their progress soon.

After these very positive updates, I would like to thank all EMWA's volunteers and to express to our members my best wishes for happy holidays and a good start in the New Year!

**Tiziana von Bruchhausen**

# EMWA News

## New Webeditorials

Webeditorials are opinion pieces published online that touch on a topic related to medical writing. A webeditorial may be serious or light and descriptive or opinion.

EMWA's webeditorials can be found at <https://www.emwa.org/about-us/emwa-news/web-editorial/>.

Three new webeditorials were published recently:

- Jack Aslanian muses about the life and death of words in a thought-provoking article
- Amadora Díaz-Palacios tells how she got into medical writing in a personal account
- And in his second contribution, an issue of *Le Parisien* caught Jack Aslanian's attention...and that of many people in France with an interest in alternative medicine



## Statement on the UK withdrawal from the EU and its impact on clinical trials

On September 6, the European Commission Directorate-General for Health and Food Safety published a statement on the UK withdrawal from the EU and its impact on clinical trials. The statement discusses the main consequences of the UK withdrawal from the EU, which include:

- supply of investigation medicinal products;
- establishment requirements for the sponsor or the legal representative; and
- submission of clinical trial information

The statement is available at [https://ec.europa.eu/info/sites/info/files/notice\\_to\\_stakeholders\\_brexit\\_clinical\\_trials\\_final.pdf](https://ec.europa.eu/info/sites/info/files/notice_to_stakeholders_brexit_clinical_trials_final.pdf).



## Why you shouldn't miss the next EMWA conference in Vienna

EMWA's spring conference will be held in Vienna, Austria, in May 2019. If you are not yet sure whether you should register or not, listen to Carolina Rojido's thoughts after her first conference and Laura Collada's discussion of why attending conferences is so useful on EMWA's YouTube channel at <https://www.youtube.com/channel/UCkaSwnvUozkgCiknWeysYA>.



## Delphi study participation

EMWA members were invited to contribute to the development of a new outcome reporting standard for clinical trial protocols and reports of completed trials, called the Instrument for reporting Planned Endpoints in Clinical Trials (InsPECT).

A need was identified for internationally harmonised and comprehensive guidance applicable to all outcome types, disease areas, and populations for reporting outcomes in clinical trial protocols and reports.

Inadequate and poor-quality outcome reporting in clinical trials is a well-documented

problem that impedes the ability of researchers to evaluate, replicate, synthesise, and build upon study findings and affects evidence-based decision making by patients, clinicians, and policy makers.

To improve clinical trial reporting quality, reporting guidelines have been developed for clinical trial protocols (SPIRIT) and completed trials (CONSORT and CONSORT extensions). InsPECT will build upon these guidelines through two evidence-based reporting extensions, one specific to trial protocols (SPIRIT-InsPECT Extension) and one specific to trial reports

(CONSORT-InsPECT Extension).

This project is funded by the Canadian Institutes of Health Research. InsPECT is led by Drs. Nancy Butcher, Martin Offringa, An-Wen Chan, and David Moher, and more information can be found on the InsPECT website at <http://www.inspect-statement.org> and on Twitter: @InsPECT2019.

The protocol for InsPECT development and project details are publicly available on the Open Science Framework at <https://osf.io/arwy8/>. Anonymised project data will also be made publicly available here.

## Updated NewsBlast instructions to contributors



Contributions to the NewsBlast should be sent to [pr@emwa.org](mailto:pr@emwa.org) by the 22nd of each month so that it can be published in the following month. Updates should be concise (150-200 words) and can be included on one of the EMWA webpages.

The full archive of EMWA NewsBlasts can be accessed at <https://www.emwa.org/about-us/emwa-news/>.

## Best attended EMWA November conference of all time!

A total of 214 attendees (a record number for an EMWA November conference) made their way to the 47th EMWA Conference in Warsaw in early November. There was a large proportion of first-time attendees, some 95 in all. All of the delegates attended some of the 31 workshops on offer, 8 of which were completely full.

In addition to the workshops, the conference offered a number of events outside of the formal education programme, such as the traditional networking reception, freelance business forum, early morning yoga, as well as a free seminar entitled "Introduction to Medical Writing" and daily interactive short seminars for a quick "English" fix looking at

major and minor issues with the use of English led by Alistair Reeves. On Friday evening there were a number of social events. These were attended by 95 old and new EMWA friends.

The opening session was led by Tiziana von Bruchhausen, the current EMWA president, and Slávka Baróniková, the EMWA conference director. A CORE Reference update was given by Sam Hamilton and Art Gertel.

Artur Dziejewicz then gave an entertaining presentation about the past, present, and future of Polish cardiology and cardiac surgery. The city of Warsaw was introduced by Maria Kołtowska-Hägström and Anna Reichel. Their talk was accompanied by some wonderful photography.

# Measuring health outcomes: The foundation of contemporary healthcare decision-making

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## Abstract

Healthcare professionals and patients are (or should be) interested in understanding the benefits of health care. We should be able to know the expected treatment benefits and to see quantifiable evidence that supports those expectations. Such information is a requirement in all clinical studies and there have long been calls for the systematic recording of health outcomes. Without such information how will healthcare professionals differentiate between treatments that yield health benefits – and those that do not? Key to the measurement of outcomes in healthcare is an understanding as to what is meant by “health”, a concept that continues to evade a universally agreed definition. The measurement of health outcomes provides three key pieces of information – it identifies whether or not anything has changed, the direction of any change and its magnitude. New approaches to measuring health outcomes herald new ways of managing and delivering healthcare in the twenty-first century.

Whether as health professionals delivering care or as patients receiving it; whether as researchers working at the frontiers of science or administrators working in healthcare provider units – all of us are directly or indirectly interested in health, if not currently then with increased likelihood as we grow older. But what



exactly is meant by “health”? How is it defined? It is paradoxical that this universal concept lacks a universally agreed understanding of its meaning. This is in marked contrast to the physical parameters that characterise the science that underpins the practice of healthcare itself. Standardised units of measure are found everywhere, from body weight to blood pressure, lung function, nerve signal transmission, cardiac output, blood chemistry. The 1946 Constitution of the World Health Organization (WHO)<sup>1</sup> opens with a definition of health as “state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”, but this raises many other questions, for example what is meant by “well-being” and how can we establish when it is “complete”? The three nominated facets of health included within the WHO

definition make no allowance for cultural and ethnic factors that need to be taken into account when thinking about health. Traditional Chinese medicine recognises many signs and symptoms that have significance in establishing a patient’s health status, but which are discounted by physicians trained elsewhere. Social organisation, practice and values change over time allowing new health-related issues to emerge. Contraceptive practice, gender identity, cosmetic appearance, domestic violence are recent additions to the health lexicon. At one level all such considerations could be judged to be philosophical, but healthcare today relies predominantly on empirical evidence and in order for us to measure it, we need clarity about what it is that we are observing and agreement about the

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metrics to be used to quantify those observations.

For the purposes of what follows here, it is necessary only to accept the principle that we can (and should) think about health as a quantifiable concept. Several different approaches of varying degrees of legitimacy have been proposed for measuring health, but none has acquired the distinction of being recognised as the standard. All forms of measurement begin with description. Diagnostic systems such as ICD-11 represent a sophisticated mechanism through which we can define the health (or rather ill-health) of a patient.<sup>2</sup> An individual patient can be categorised with a diagnostic code or codes, establishing information which can be important in its own right. Knowledge of a diagnosis can help guide decisions about clinical investigation and treatment. By aggregating data based on ICD codes we can establish the prevalence of conditions of interest in the population at large. Even at the level of the hospital or provider unit we can use such information to compare workload and monitor performance.

More than 150 years ago, Florence Nightingale published a classification of health status that was to be applied to all patients leaving her care.<sup>3</sup> This system that describes patients as being *relieved* (better), *unrelieved* (same), or *dead* has a level of sophistication that continues to challenge us all today, namely the ability to systematically identify and record patient's status following treatment. A fundamental question that is central to all healthcare decisions, for individual patients or collectively for a population, is that of deciding whether healthcare interventions “work”. There is an understandable tendency to always see healthcare in a positive light. Nothing stimulates a community more than the threatened loss of a local healthcare service, but against a background of limited resources (including personnel, capacity and budgets) there is a need to assess evidence regarding the effectiveness and cost-effectiveness of healthcare interventions.

Advances in medical practice do sometimes come with undesirable consequences. A recent UK study of medical device-related pressure ulcers revealed more than 7,200 cases of iatrogenic harm, i.e., harm caused by a medical intervention or investigation.<sup>4</sup> Well-established practice too is not without its risks. A Canadian study<sup>5</sup> of older

patients admitted for in-patient care found that acute illness and hospitalisation are associated with significant potential harm notably from so-called “pyjama paralysis” in which patients remain confined to bed rather than being mobilised. Sometimes healthcare systems fail. In 1998, a UK general practitioner was found guilty of the murder of more than 200 of his patients.<sup>6</sup> A review of perioperative deaths published in 1987 identified organisational shortcomings that adversely affected patient outcomes but also instances of terminally ill patients undergoing surgery that would not have improved their condition.<sup>7</sup>

In considering the role of health outcomes, we need first to understand why it is that we provide health care in the first place. In its most dramatic form we can see how interventions might save lives; beyond that we might expect health care to relieve symptoms, to maintain or improve aspects of function and potentially to extend life through early detection. Generally speaking, we intervene with patients in order to improve the expected trajectory of

health that would otherwise occur without it. Sometimes there is a clear association between the intervention and the expected benefits so that we can observe and quantify the extent to which changes occur. Much depends, however, on the nature of the benefits. Relieving the painful effects of arthritis could be easily classified as being a health benefit, but there is less consensus about, say, providing cosmetic surgery for the removal of unwanted tattoos where the benefits might be regarded as being largely non-health in nature. This returns us to the unanswered issue concerning a definition of health. Indeed, the issue is much wider than one might suppose since the boundaries of healthcare are subject to change, most obviously when dealing with older citizens who present with health *and* social care needs. There is increasing interest in broadening the focus from a relatively narrowly defined concern with health to that of quality of life, well-being, life satisfaction or happiness; all of these share the same limitations of being ill-defined and lacking any standard method for their observation.

In the 1900s early proponents such as Ernest Codman proposed what we now call health outcome measurements Donabedian<sup>8</sup> described “end results hospitals” in which patients are

followed up “long enough to determine whether the treatment given has permanently relieved the condition or symptoms complained of”.<sup>9</sup> Archibald Cochrane in his seminal monograph on efficiency and effectiveness declared that we should always “assume that a treatment is ineffective unless there is evidence to the contrary”.<sup>10</sup> For many conditions there exist disease classification systems that are widely used to represent patient health status but which in fact describe disease staging. Systems such as the TNM and Dukes classification in colon cancer are typical and categorise patients solely in terms of their disease. They are silent with respect to all other aspects of the patient experience and although they are readily understood by clinicians such indicators are at best only partial indicators of patient health. The clue here lies in the use of such indicators. Clinicians are by virtue of their training and experience likely to assess a patient's health status in terms of the parameters that they have grown accustomed to handling. The patient for their part may judge their condition or illness from an entirely different perspective. Neither viewpoint is correct; neither dominates the other.

If we understand the rationale for intervening, then we should be able to select a target metric that we expect to influence; if we then track that metric over time we will be able to derive quantifiable evidence of “health” outcomes in terms of its direction and magnitude. For example, in tackling obesity a planned weight loss programme may result in measurable change expressed in terms of standardised units of measure. In such a situation we would need to weigh the patient before and after the intervention using the same weighing machine at both time points. We can then use these observations to compute the *difference* in weight. The sign of that difference indicates the *direction* of change and the arithmetic difference indicates the *magnitude* of that change. These then are the basic attributes

A fundamental question that is central to all healthcare decisions, for individual patients or collectively for a population, is that of deciding whether healthcare interventions “work.”





of all measures of health status.

The development of new approaches to the measurement of health status had its origins in the mid-1960s, reflecting growing concern about the superiority of the healthcare professional in deciding such matters. New terms appeared in the clinical and health services research literature, notably quality of life or more accurately health-related quality of life. Today these same measures have been relabelled under the somewhat unfortunate heading of patient reported outcomes (PROs)<sup>11</sup> – unfortunate, as these measure health status at a single point in time *not* outcomes; they can only indirectly assess outcomes since they require repeated (before/after) observations from which we subsequently infer a change in health status.

Defined originally as being “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” PROs mirror the growing recognition of the patients’ voice in measuring the benefits of treatment. The most important feature of this class of measures is that information should come directly from the patient. This requirement has far-reaching implications – most notably for health economists. The evaluation of treatment in the twenty-first century is not restricted to questions of safety and efficacy but has to be seen in a wider context. There are inevitable limits to all healthcare systems and there is widespread acceptance of the need for evidence of cost-effectiveness to help inform decisions and to set priorities. Measuring health outcomes is fundamental to such cost-effectiveness analysis and health economists have placed their own technical requirements on how health benefits should be described and valued. In particular, they hold to a position that the value of health outcomes should be determined by the society as a whole – *not* by patients or others who might be classed as beneficiaries. What was already a volatile cocktail of ill-defined concepts

has now become an ever more complex science with competing views about its own technology.

However, at its core, health outcome measurement, which we can define as being “a quantifiable change in health status resulting from the provision or withholding of healthcare”, is a process of observation that is common to all those concerned with the planning, financing, management, and delivery of healthcare. It is an integral part of all clinical studies and helps guide investment decisions made by pharmaceutical companies. It provides information that should be available to patients and consumers of healthcare. Absorbed into routine clinical practice it provides intelligence that can help refine decisions about preferred treatment options; the absence of health outcomes data creates space for the continuation of clinical practice of unproven benefit. In short, the need for health outcome measurement has never been greater and its potential value is limited only by the creativity and imagination of those willing and able to generate it.

### Conflicts of interest

The author is a founder-member of the EuroQoL Group.

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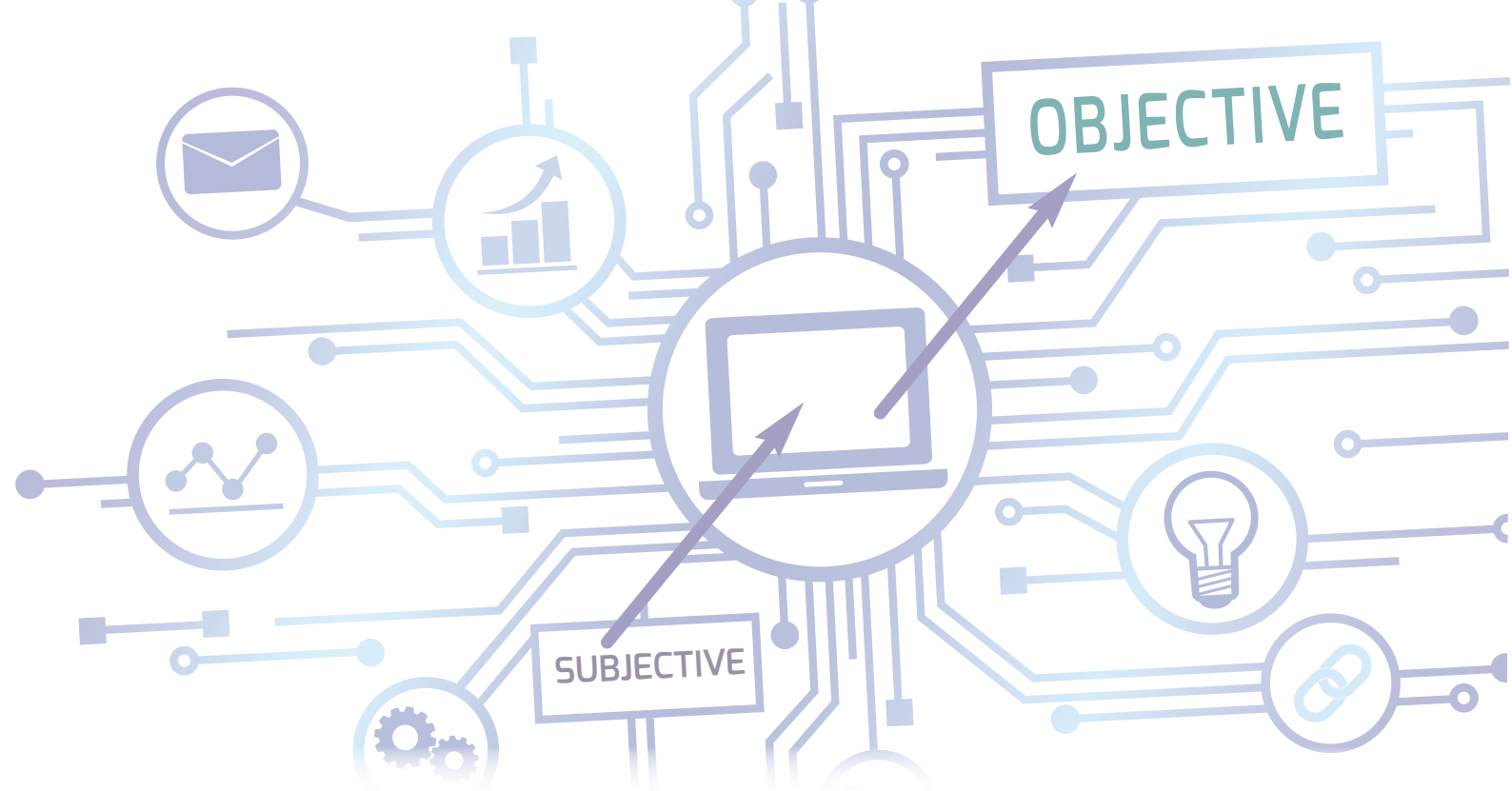
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# Measuring quality of life – theoretical background

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## Abstract

Patient-centred medicine has come out of the increasing importance of patients’ voices in disease management. As part of this, health-related quality of life (HR-QoL) has become an important part of assessing treatment outcome and the quality of patient management. In this article, I discuss health as one of the determinants of a good quality of life and how to interpret and present HR-QoL measures and thereby place them in a clinical context. Key issues covered include the theoretical HR-QoL models underlying HR-QoL measures, how the measures are constructed, how they work, and how to interpret the scores they generate.

*Socrates: . . . And I should like to know whether I may say the same of another proposition – that not life, but a good life, is to be chiefly valued?*

*Crito: Yes, that also remains.*

– *From Crito; The collected works of Plato*



Humans have always desired to live a good life, that is, to enjoy a high quality of life (QoL), although what this means is very different for each of us. As illustrated by the QoL index, developed by *The Economist* Intelligence Unit,<sup>1</sup> QoL is complex and encompasses many aspects of life. The index includes material well-being, health, political stability and security, family life, community life, climate and geography, job security, political freedom and gender equality (Figure 1). In this article, I discuss only one of these determinants – health – in other words, the application of QoL to medicine, often referred to as health-related QoL (HR-QoL). I also present a few QoL models relevant to HR-QoL and describe the main ways to measure HR-QoL.

## Health-related quality of life

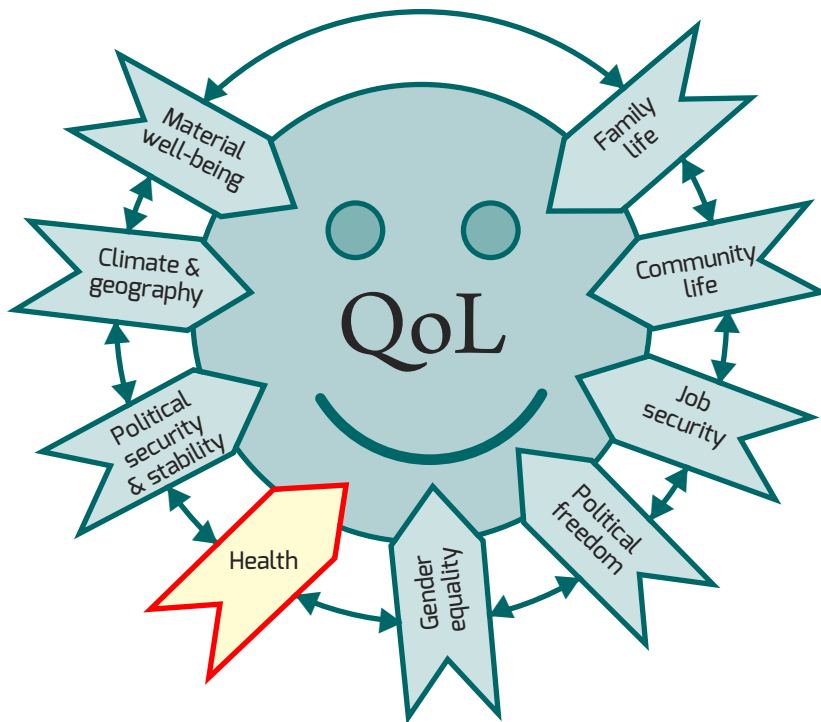
The World Health Organization defines health as “a state of complete physical, mental and social

well-being, and not merely the absence of disease or infirmity”.<sup>2</sup>

Although this definition does not include HR-QoL, it clearly includes different aspects of well-being as principal attributes of full health. In the context of this definition of health, the notions of HR-QoL and health status are closely interrelated and should not be considered separate.

According to the International Society for Pharmacoeconomics and Outcomes Research, HR-QoL is “a broad theoretical construct developed to explain and organise measures concerned with the evaluation of health status, attitudes, values, and perceived levels of satisfaction and general well-being with respect to either specific health conditions or life as a whole from the individual perspective”.<sup>3</sup> More specific examples of QoL aspects (also known as “dimensions”) are described by Fayers and Machin:<sup>4</sup>

- General health with a focus on functional status both physical and emotional;
- Checklists of symptoms;
- Daily living activities;
- Personal well-being;
- Sexual functioning; and
- Impact of illness on social, emotional, and family functioning.



**Figure 1. QoL – index developed by The Economist Intelligence Unit.**  
 Modified from Koltowska-Hägström et al. 2009.<sup>17</sup>

The authors, therefore, conclude that HR-QoL is a multidimensional construct. They also emphasise that subjectivity is a basic and unquestionable feature of HR-QoL so that it can be evaluated only by patients themselves. The only exceptions to this are for patients who are incapable of providing information, for example, small children, patients with communication problems, or patients intellectually incapable of effectively responding. For such cases, proxy measures are acceptable.<sup>5</sup>

**QoL models**

A variety of HR-QoL models have been proposed and are the basis for various HR-QoL

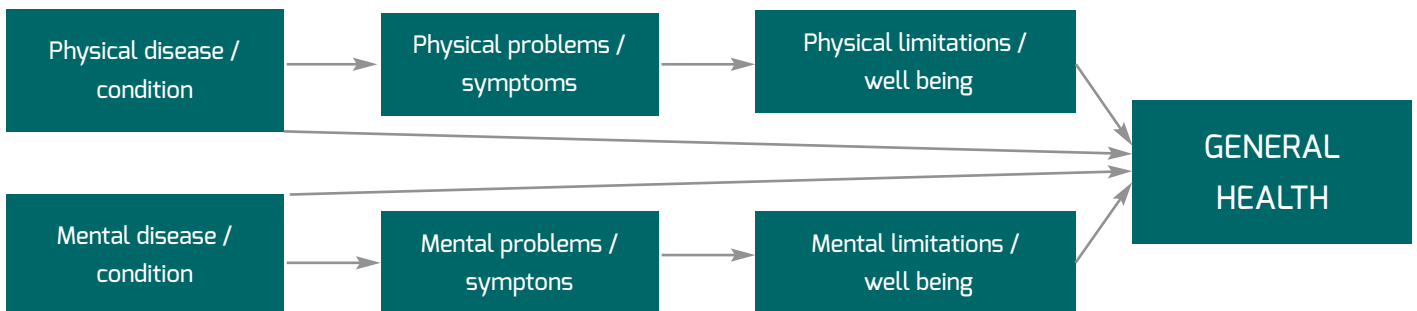
measures. One of the first models was developed by Ware,<sup>6</sup> who specified three generic health concepts: physical health, mental health, and general health, which he placed on a continuum (Figure 2). Briefly, physical conditions are closely linked to physical symptoms. These lead to physical limitations and reduced well-being. Similarly, mental conditions relate to mental symptoms and consequently cause psychological distress and poor well-being. Both physical and mental conditions can severely impair perceived general health. This model underlies the SF-36 (36-Item Short Form Survey),<sup>4</sup> one of the most commonly used HR-QoL measures.

Another continuum-based model of QoL was

developed by Wilson and Cleary<sup>7</sup> who highlighted increasing complexity when moving from biological and physiological factors (the lowest level) through symptoms, functioning, and general health perceptions to overall QoL (the highest level) (Figure 3). Throughout different levels, their model also incorporates relationships and other factors, such as characteristics of the individual and the environment and non-medical factors.

In 1965, Nagi introduced the first disablement model including active pathology, impairment, functional limitation, and disability (Figure 4), thus starting a new family of models. In this model, impairment is a structural abnormality at an anatomical level (cells, tissues, organs); functional limitation indicates a difficulty in performing activities; and disability is categorised as physical, mental, social, or emotional and covers the ability of a person to fulfilling role in life. Nagi’s main contribution to patient-centred medicine was to move the concept of disability away from pure physical dysfunctions to interactions between the patients and their environment. More recent disablement models, such as those of the National Center for Medical Rehabilitation Research Disablement Model and the World Health Organization International Classification of Functioning Model, are rooted in Nagi’s concept.<sup>8</sup>

Calman’s expectation model<sup>9</sup> assumes that QoL reflects the distance between individual’s present experience and expectations (Figure 5). In this model, a smaller gap corresponds to a better QoL, and QoL can be enhanced by improving the current situation, for example by treating disease or modifying expectations. The Evaluation of Individual Quality of Life (SEIQoL) and the Patient Generated Index are



**Figure 2. HR-QoL model proposed by J. R. Ware**  
 Modified from Ware et al. 1995.<sup>6</sup>

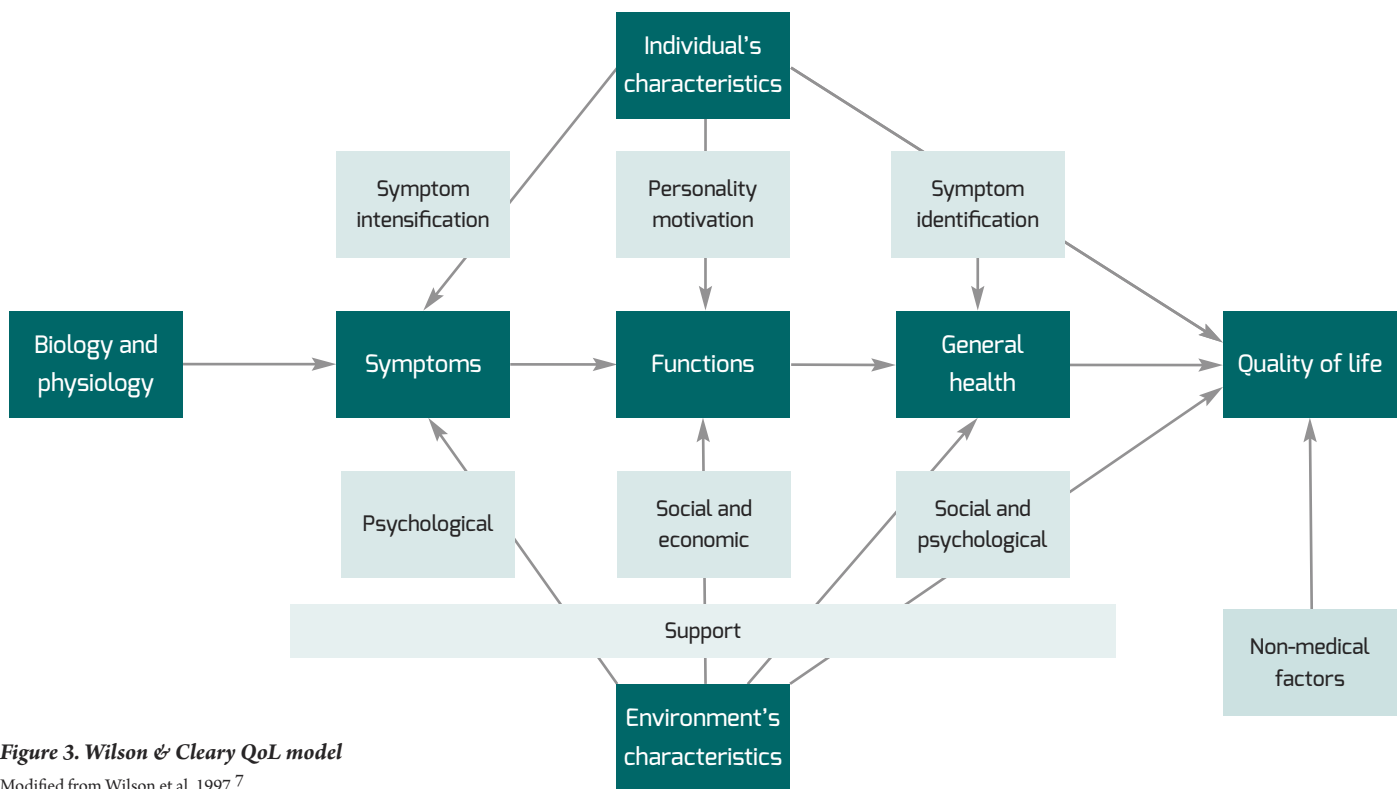


Figure 3. Wilson & Cleary QoL model

Modified from Wilson et al. 1997.<sup>7</sup>

based on Calman's model.<sup>4</sup>

A similar rationale applies to the need-based model, in which QoL depends on the personal capacity to satisfy human needs. In this model, poor health interferes adversely with satisfying needs, and thus has a negative impact on QoL. Nevertheless, this model assumes that as long as the primary needs are fulfilled, for example, by compensation mechanisms, QoL remains unchanged.<sup>10</sup> Examples of need-based measures are the QoL-AGHDA (QoL-Assessment of Growth Hormone Deficiency in Adults) and the QLDS (QoL in Depression Scale).<sup>11</sup>

## Item structure, scales, and scores

### Item structure – index and profile

HR-QoL measures are built from items (questions or statements) and can contain just one (single-item measure) or several (multi-item measure). The items in multi-item measures can constitute one dimension (unidimensional) or more (multidimensional). Depending on the item structure, HR-QoL measures produce two types of scores: an index or a profile. Single-item measures generate an index (a single number), whereas multi-item measures generate a profile or an index. Profiles are represented by a set of scores for each measured dimension (subscale).

They provide more detailed information about the characteristics of HR-QoL and enable better understanding of the problems respondents are facing.<sup>4</sup> Therefore, profiles are suitable for clinical practice, although they may not be able to capture an overall change in HR-QoL (magnitude and direction). The NHP (Nottingham Health Profile) is a good example of a multi-dimensional measure: it includes sleep, pain, emotional reactions, social isolation, physical mobility and energy level.<sup>12</sup> For some profiles, a simple sum of dimension scores is accepted, although their accuracy is questionable because the calculation assumes equal importance of each dimension, which is often not the case. This problem can be overcome by applying weights, which are relative values for each dimension (or even item). Derived in this way, a

single aggregated score is believed to be robust and appropriate.<sup>5</sup> For NHP, an index can be computed based on weighted or unweighted dimension scores.<sup>13</sup>

### Scales and scores

Information is collected in different ways by HR-QoL measures. Many but not all are based on an ordinal scale. The simplest are dichotomous variables describing health status (e.g. non-diseased/diseased) or by a yes/no answer for specific problems. This is often used to construct need-based measures. For these, the score can be generated by simply summing up the number of "yes" answers, in other words, the number of recognised problems. Therefore, a higher numerical score denotes poorer HR-QoL, and a decrease in the score indicates improve-

When interpreting and writing up data generated with a Likert's scale, its ordinal properties and its subjectivity must be considered.

It is also critical to understand how the choices are coded, that is, whether a higher score indicates better or worse HR-QoL and whether an increase indicates improvement or deterioration. Finally, when comparing results originating from different HR-QoL measures, it is important to check whether working scores or scale scores are used.

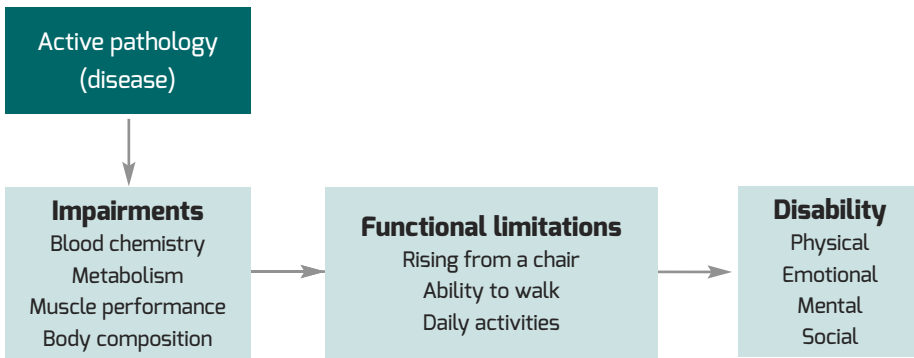


Figure 4. Nagi's disablement model

Modified from Woodhouse et al. 2006.<sup>18</sup>

ment.<sup>12</sup> Such a descriptive classification distinguishes between different categories and orders them hierarchically.

**Likert scale**

The most frequently used scales for measuring QoL are ratings like Likert's scale<sup>14</sup> and the visual analogue scale (VAS). Likert introduced his scale in 1932 to measure social attitudes in the US. The items he included, particularly in the "Negro scale", are nowadays considered shocking, but the way he proposed to collect information is widely used. Likert's scale contains one or more items (statements), each linked to several choices, usually ordered from the lowest to the highest level, for example, worst/not important at all/never/completely disagree and best/extremely important/always/fully agree, with intermediate choices in between (Figure 6). Although five options are usually used for most items, the

number can vary from three to nine. An odd number of choices is recommended to allow for a "neutral" choice. For analysis, the choices are coded as sequential numbers, for example, from 1 for worst to 5 for best. These numbers are summed to generate a single score (index). Sometimes the raw (working) score is standardised to a scale 0 of 100 to facilitate comparisons between different measures. Such a standardised score is called the "scale score", and the standardisation to a 100-point scale is referred to as "the standard scoring method".<sup>4</sup> Because the scale is ordinal, it does not have a well-defined unit of measurement, and it can only indicate a direction of a change but not its magnitude. For example, the distance from "not important at all" (1) to "little important" (2) is not necessarily the same as between "little important" (2) and "important" (3)". In other words, the change from (1) to (2) does not need to be equal to the

change from (2) to (3).<sup>5</sup> When interpreting and writing up data generated by a Likert's scale, its ordinal properties and its subjectivity must be considered. It is also critical to understand how the choices are coded, that is, whether a higher score indicates better or worse HR-QoL and whether an increase indicates improvement or deterioration. Finally, when comparing results originating from different HR-QoL measures, it is important to check whether working scores or scale scores are used.

**Visual analogue score**

The linear analogue self-assessment, now referred to as the VAS, was first used by Priestman and Baum to measure HR-QoL in patients with breast cancer.<sup>15</sup> It consists of a 100-mm horizontal or vertical line on which a respondent places a mark in response to a question (Figure 7). A VAS is anchored at one end by the lowest choice (e.g. worst possible/never/not important at all) and the other by the highest choice (e.g. best possible/always/extremely important). The score is computed as the measured distance from the left end to the respondent's mark. Thus, the VAS is a continuous scale that generates a single score.<sup>16</sup>

**Conclusion**

Patient-centred medicine has come out of the increasing importance of patients' voices in disease management. As part of this, HR-QoL has become an important part of assessing treatment outcome and the quality of patient management. Understanding the theoretical background and basic rules governing HR-QoL research is essential for being able to correctly interpret and present HR-QoL data. In other words, one must understand what the numbers mean and remember that for HR-QoL, 2 + 2 is not always 4 and 2 is sometimes more (better) than 3!

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**Conflicts of interest**

The author declares no conflicts of interest.

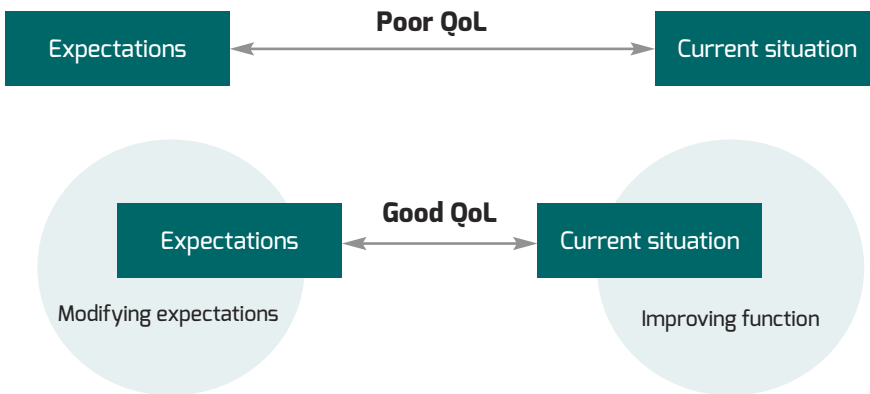


Figure 5. Calman's QoL expectation model

Modified from Calman et al. 1984.<sup>9</sup>

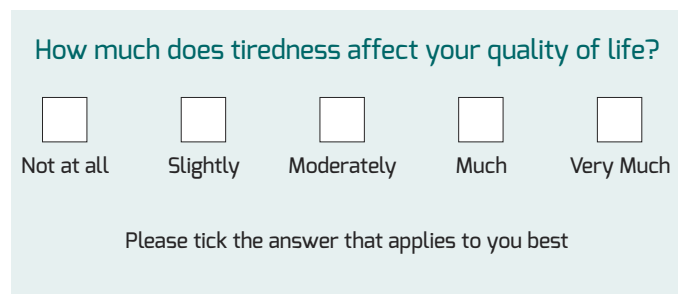


Figure 6. Example of a Likert scale

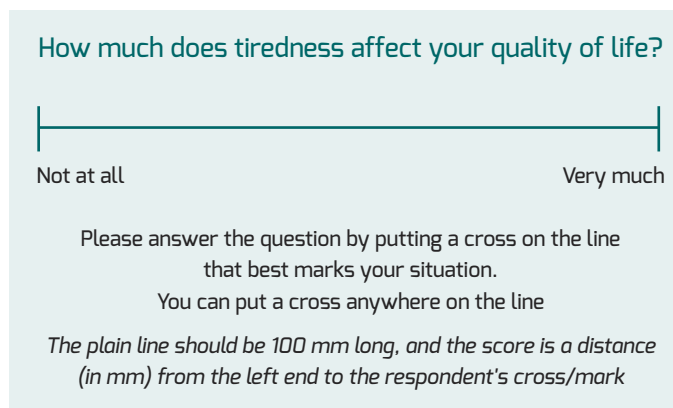


Figure 7. Example of a visual analogue scale (VAS)

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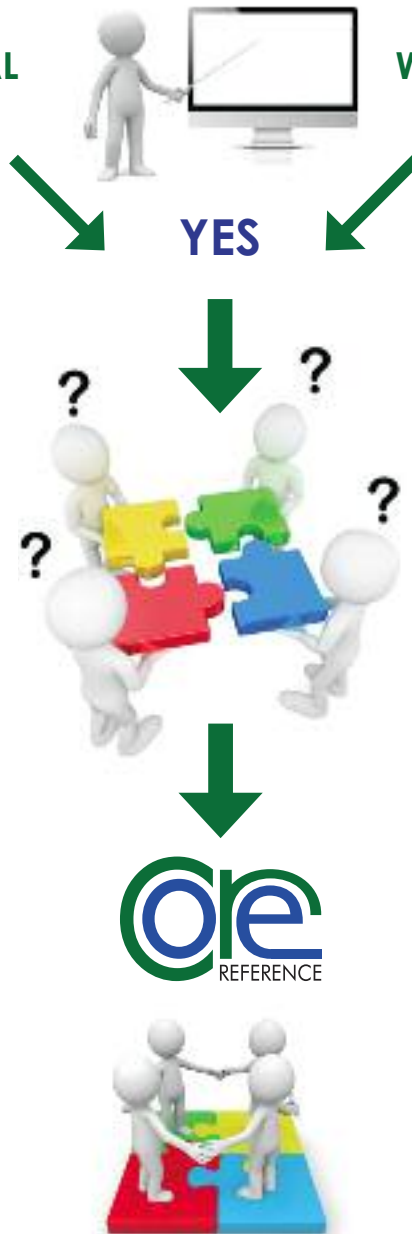
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# Quality of life measures – an overview

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## Abstract

HR-QoL measurements attempt to turn subjective information into objective information. In this article, I describe the different kinds of health-related quality of life (HR-QoL) measures, how they work, and how they can be interpreted. Main types of HR-QoL measures include generic; disease- or population-specific; dimension-specific; individualised; and preference-based. Each serves different purpose and should be applied to different populations. For example, generic measures can be used in general populations and across various diseases, whereas disease-specific ones address specific diseased populations. I also discuss key considerations for using and presenting HR-QoL measures, including ensuring that a validated and legally obtained measure is administered; describing the type and specifics of the HR-QoL measure; and explaining how the measure was used, how scores were computed, and how to interpret them.

Health-related quality of life (HR-QoL) belongs to the family of patient-reported outcomes. HR-QoL measurements attempt to turn subjective reports into objective data. This requires properly developed and well-validated measures, developed following well-defined and strict rules, such as those described in the *Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, published by the US FDA in 2009.<sup>1</sup> Developing HR-QoL measures is laborious, time-consuming, and requires a highly skilled and knowledgeable team of researchers.

In this article, I describe the different kinds of HR-QoL measures, how they work, and how they can be interpreted. Depending on the purpose of measuring HR-QoL and the target population, HR-QoL measures are categorised as generic; disease- or population-specific; dimension-specific; individualised; and preference-based. Preference-based measures are sometimes referred to as “utility measures” because they primarily serve to generate utilities, a unit used in health economic evaluations, although utilities can also be derived from certain generic and disease-specific measures.<sup>2</sup> Furthermore, some measures can fall into two categories; for example, dimension-specific measures, which can be used in general population as well as across different diseases, can also be considered generic.

## Generic HR-QoL measures

Generic HR-QoL measures are designed for use in any population, irrespective of disease status, that is, in patients regardless of the condition they suffer from and in general populations. Many generic measures focus on physical function and measure impairment, disability, or handicap. Others cover psychological issues. Although they are often considered as not being sensitive enough to detect changes specific to certain diseases, they allow comparisons across different conditions and with general populations. The most widely used generic measures are EQ-5D, the SF-36 (36-Item Short Form Survey) and the NHP (Nottingham Health Profile).

### EQ-5D

The EQ-5D defines five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety or depression.<sup>3</sup> In the original version of the EQ-5D, currently referred to as EQ-5D-3L, each dimension is categorised into three levels of burden: 1) no problem, 2) a moderate problem, and 3) an extreme problem. The respondents first indicate the level of burden that applies to their situation and then record their perception of their general health state on the EQ-VAS (EQ-visual analogue score). The EQ-5D is available in more than 170 languages<sup>4</sup>



and is being used in many clinical and economic studies as well as population surveys all over the world. Over the years, the measure has evolved and now two other versions are available – the EQ-5D-5L (Figure 1) and the EQ-5D-Y. The EQ-5D-5L was introduced in 2009 to increase sensitivity and reduce ceiling effect over the EQ-5D-3L. It contains two intermediate categories of burden: slight and severe. The EQ-5D-Y targets children and adolescents aged 8 to 15 years and is also available as a proxy measure. All EQ-5D measures can be administered as a paper or electronic version.<sup>5</sup> To use any of EQ-5D measures, a planned study or project needs to be registered at <https://euroqol.org/support/how-to-obtain-eq-5d/>, and the conditions of use agreed upon with the EuroQol EuroQol Research Foundation Office.

**SF-36**

The SF-36 measures physical and mental health as well as provides assessment of general health.<sup>6</sup> Physical health includes physical functioning (10 items), physical role functioning (4 items), bodily pain (2 items), and general health (6 items). Mental health includes vitality (4 items), emotional role functioning (3 items), social role functioning (2 items), and mental health (5 items). For most items, Likert’s scale is

used. The SF-36 is available in shorter versions, such as SF-6D, SF-12, and SF-20, of which the SF-6D is used primarily in health economic evaluations. These measures are in the public domain and free-of-charge, although certain legal conditions are imposed, for example, proper acknowledgement. They can be downloaded from [https://www.rand.org/health/surveys\\_tools.html](https://www.rand.org/health/surveys_tools.html). Following the instructions for calculating the scores is crucial because items for physical and mental health are constructed in opposite directions. The raw scores from the SF-36 can be standardised on a 100-point scale, assuming equal weighting for each item. For some countries, such as Germany, country-specific weights are available and should be used for national data.<sup>7</sup> Overall, a lower score denotes poorer HR-QoL.

**Nottingham Health Profile**

The NHP (Figure 2) is another example of a generic measure. It focuses on feelings and emotions, rather than physical performance, and includes 38 items (statements) in six dimensions, as explained in the accompanying

article “Measuring Quality of life – theoretical background” in this issue of *Medical Writing* (page 8).<sup>8</sup> The respondent selects “yes” or “no” according to whether a certain problem applies. The score is calculated by adding the number of “yes” answers (i.e., the number of recognised problems). Thus, a higher score denotes poorer HR-QoL. Galen Research is the copyright holder and should be contacted at <http://www.galen-research.com> to request permission for its use.

Disease-specific measures are developed to address the need to monitor patients with increased accuracy and to provide enough sensitivity to detect features of specific conditions.

**Disease/population-specific measures**

Disease-specific measures are developed to address the need to monitor patients with increased accuracy and to provide enough sensitivity to detect features of specific conditions. Currently, many disease-specific measures targeting various patient populations are available.

**EORTC QI-C30**

One of the first disease-specific HR-QoL

Under each heading, please tick the ONE box that best describes your health TODAY.

**MOBILITY**

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

**SELF-CARE**

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**PAIN / DISCOMFORT**

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

**ANXIETY / DEPRESSION**

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

2

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We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

100 means the **best** health you can imagine.

0 means the **worst** health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health you can imagine

100

95

90

85

80

75

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

The worst health you can imagine

3

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I would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health you can imagine

100

95

90

85

80

75

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20

15

10

5

0

The worst health you can imagine

1

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Figure 1. EQ-5D-5L – sample

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Figure 2. Nottingham Health Profile (NHP) – sample

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**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: \_\_\_\_\_

Your birthdate (Day, Month, Year): \_\_\_\_\_

Today's date (Day, Month, Year): \_\_\_\_\_

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
<b>During the past week:</b>				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in doing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you lost weight?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page.

**Figure 3. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 – sample**

Accessed from: <http://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf>

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measures was the EORTC QLQ-C30, developed by the European Organisation for Research and Treatment of Cancer (EORTC) for patients with cancer (Figure 3).<sup>9</sup> The EORTC QLQ-C30 is multidimensional and encompasses five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea/vomiting); a global health status/HR-QoL scale, a number of single items such as dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea; and an assessment of economic impact of the disease. Responses are given on Likert's scale, with a different number of choices for different items. The EORTC QLQ-C30 is copyrighted by EORTC (<http://groups.eortc.be/qol/eortc-qlq-c30>).<sup>10</sup> A manual is provided for computing and standardising scores, but in general, the scores for all scales and single items range from 0 to 100, with a higher score corresponding to greater response. Practically, this means that a higher score for a functional scale and for global health status/HR-QoL correspond to better function and HR-QoL; however, a higher score for symptoms indicates more or more severe symptoms or problems.<sup>11</sup> The EORTC QLQ-

**KINDL**

**Information**

**Questionnaires**

**Terms of Usage**

**Manual**

**Analysis**

**Language versions**

**Reference/norm values & validation**

**Publications**

**CAT-SCREEN**

**Information**

**Procedure**

**Analysis**

**Demo version**

**Links**

**Contact**

**Demo version**

Click on the little pictures to enlarge!

In der letzten Woche habe ich mich krank gefühlt.

In der letzten Woche habe ich mich viel gelacht und Spaß gehabt.

In der letzten Woche fand ich mich gut.

In der letzten Woche habe ich mich zuhause wohl gefühlt.

In der letzten Woche machten mich die anderen Kinder.

In der letzten Woche habe ich mich auf die nächsten Wochen gefreut.

Bist du gerade im Krankenhaus?

Hast du eine längere Krankheit, wie z.B. Grippe, Allergie, Neurodermitis, Diabetes oder so?

Bist du in der letzten Woche krank gewesen?

Oder bist du ganz gesund?

Das hat mir lange.

Du bist so schön!

Du hast so tolle Sachen!

Du lachst so schön!

Du bist so nett!

Liebe Grüße

**Figure 4. CAT screen**

Accessed from <https://www.kindl.org/english/cat-screen/demo-version/>. Reprinted with permission from KINDL.

C30 is modular: the core addresses the issues generally encountered by patients with any cancer, and specific modules are included for different types of cancer or their treatment.

**AcroQoL**

Another example of a disease-specific measure is the AcroQoL (Acromegaly Quality of Life Questionnaire).<sup>12</sup> It contains 22 items describing problems experienced by patients with acromegaly. The items cover three dimensions: physical, psychological/appearance, and psychological/personal relations. Responses are based on Likert's scale, and depending on the item, choices for frequency or the degree of agreement with the problem described, are coded from 1 to 5. The raw scores for each item are summed and then standardised to a scale of 22 to 110, with a higher score corresponding to a better HR-QoL.

**HR-QoL in children and adolescents: KINDL and CAT-SCREEN**

Interest in HR-QoL measures for the paediatric population is growing, and many measures have been or are being developed. KINDL®, originally developed by Monika Bullinger in 1994 assesses HR-QoL in healthy or diseased children and adolescents aged 3 to 17 years.<sup>13,14</sup> In addition to the core generic module, several disease-

specific modules have been developed, such as for paediatric patients with asthma, epilepsy, cancer, diabetes, or obesity. The core measure contains 24 items and is provided in three versions for different age groups (4-6, 7-13, and 14-17 years), each of which can be completed by a child or adolescent and their caregiver. KINDL is available as a paper-pencil version and an electronic version called CAT-SCREEN (Figure 4).<sup>15</sup> All versions are copyrighted.

**Dimension-specific measures**

Dimension-specific measures focus on certain HR-QoL domains, such as pain, fatigue, and anxiety and depression. Examples include HADS (Hospital Anxiety and Depression Scale),<sup>16</sup> the McGill Pain Questionnaire,<sup>17</sup> and the MFI (Multidimensional Fatigue Inventory).<sup>18</sup> The structure and principles of dimension-specific measures are similar to those of disease-specific ones, as described above. Depending on the nature of the items, these measures can be used for any diseased population or even for a general population and thus could be considered generic.

**Individualised measures**

Individualised measures aim at evaluating HR-QoL from respondents' own perspective and allow them to either include items of their choice

**QLS<sup>®</sup> Questions on Life Satisfaction** Hypopituitarism - USA

The following areas of health apply mainly to people with hormone deficiencies. You should indicate how **important** the individual areas are to you personally, and then how **satisfied** you are with them.

Please answer **all** of the questions. Do not be influenced by whether you feel good or bad now. Think about the **last four weeks** when answering the questions.

First please check how important each individual area is to your health. Before you begin, please read questions 1-9 below.

How important for you is (are) your....	not important	slightly important	moderately important	very important	extremely important
1. ability to handle stress.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. body shape / appearance.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. self-confidence.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. ability to become sexually aroused	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. ability to concentrate.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. physical endurance.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. initiative / drive.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. your ability to deal with anger.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. being able to stand the disturbances and noise of everyday life.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please mark how **satisfied** you are with these individual areas of your health. Think about the last four weeks, and answer all questions.

How satisfied for you is (are) your....	dis-satisfied	slightly dissatisfied	slightly satisfied	moderately satisfied	very satisfied
1. ability to handle stress.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. body shape / appearance.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. self-confidence.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. ability to become sexually aroused	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. ability to concentrate.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. physical endurance.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. initiative / drive.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. your ability to deal with anger.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. being able to stand the disturbances and noise of everyday life.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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**Figure 5. QLS-H, an example of an individualised HR-QoL measure**

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and allocate weights or to only allocate weights for predefined items. In the case where respondents include items of their own choice, they first select the most important issues relating to their HR-QoL (step 1) and then self-rate the level of problems they face (step 2). After this, they allocate weights to them (step 3). In the case where respondents use predefined items, only steps 2 and 3 are followed. The SEIQoL (Schedule for the Evaluation of Individual Quality of Life)<sup>19</sup> and PGI (Patient Generated Index),<sup>20</sup> which use all three steps, laid the groundwork for individualised measures. The administration manual for the SEIQoL, published in 1993 by O'Boyle and colleagues, describes the whole process in detail.<sup>21</sup> In principle, the scores for each item are calculated by multiplying self-ratings by allocated weights. The sum of calculated scores for each item comprises the final score (index). The QLS-H (Questions on Life Satisfaction Modules-Hypopituitarism), developed for adult patients with growth hormone deficiency, is an example of a disease-specific, individualised measure containing predefined items (Figure 5).<sup>22</sup>

## Preference-based (utility) measures

Preference-based measures emerged from



decision-making theory and are mainly used in pharmacoeconomic evaluations, also known as cost-utility analyses. The basic requirement is to incorporate patient or general population weights (utilities) for different health states assigned under uncertainty.<sup>23</sup> Utilities range from 0 (death) to 1 (perfect health), although negative numbers are possible for states considered worse than death. Utilities are used to derive QALY (quality-adjusted-life-years). A number of techniques are used to generate utilities,<sup>24</sup> such as time trade-off, as used in EQ-5D, referred to as the EQ-VT approach;<sup>25</sup> standard gamble, as used in the SF-6D (Short Form 6D);<sup>26</sup> or VAS with relevant anchors. Briefly, Time trade-off asks respondents to decide how many years of life in a described (given) condition they are prepared to give up in order to live in full health. In other words, they are asked if they prefer to live shorter in full health instead of living a certain number of years longer in a given health state or condition. Standard gamble presents alternative treatments with probabilities of better and poorer outcome to life in given health state or condition. Responders provide the highest acceptable risk of treatment failure (e.g. death). Standard gamble and time trade-off are the gold standards for measuring health utilities, but they can also be generated using a combination of standard gamble and multi-attribute scaling analysis,<sup>24</sup> as in the HUI2 and HUI3 (Health Utilities Index 2 and 3), or based on the SF-6D and the EQ-5D.

## Conclusion

HR-QoL is an important construct widely used in daily patient management, clinical trials, health economics and medical decision making. Each of these applications imposes different requirements

on the HR-QoL measures. Clinical use usually requires a measure that captures specific changes within a certain disease, within a patient population (in clinical trials), or for individual patients (in daily clinical practice). Pharmacoeconomic evaluation often requires that health status is expressed as a single summary score (a health status index) capable of identifying and quantifying differences across diseases and aggregate changes in patient health status over time. This explains why so many HR-QoL measures have been developed.

When working with HR-QoL data and writing manuscripts or other documents, medical writers should keep in mind the following:

- Most scales used in HR-QoL measures are ordinal, meaning that categories are not equally spaced.** For example, the distance from “not important at all” (1) to “little important” (2) is not necessarily the same as between “little important” (2) to “important” (3). That means that the change from (1) to (2) is not equal to the change from (2) to (3). An ordinal scale (e.g. Likert's scale) only indicates a direction of a change; it does not indicate magnitude.
- Responses and thus scores are subjective, meaning that the values behind them differ between respondents.** This depends on many different factors, such as personality, health and overall life experiences, and cultural norms.
- Understanding how a measure is constructed and how answers (choices) are coded is important when writing about them.** For example, is a higher numerical score better or worse, and does an increase in score indicate improvement or deterioration?

When writing, be sure to explain how to interpret the scores.

4. **When comparing results originating from different HR-QoL measures, check whether they are based on working scores or scale scores.**
5. **Make sure that the researchers used a legal version of a measure and that proper acknowledgement is included.** If a measure is publicly available (i.e. no licence needed), be sure to state so and acknowledge the source of the measure. Also, include information about the version number and the mode of administration needs.
6. In cases where a translation of a measure is used, confirm that it was properly translated and validated, and provide a few lines about it in the manuscript.
7. For manuscripts, follow the 2013 CONSORT-PRO extension<sup>27</sup> while presenting data from clinical trials that include patient-reported outcome measures.

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## Conflicts of interest

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# Publication planning and patient-reported outcomes: Demonstrating value in a multi-stakeholder era



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## Abstract

Patient-reported outcomes (PROs) are an essential element to demonstrate the value of a health intervention. In many ways, PROs represent the ultimate “real-world” data, yet the drive towards “Big Data” has focused on routinely collected data from healthcare databases, which often do not include assessments of PROs or the patient voice. Effective planning of PRO publications requires an in-depth understanding of the planned studies, the opportunities these provide for publications, and how clinicians, patients, and caregivers may contribute as authors to provide

validation of results. Mainstream clinical journals and conferences should be targeted wherever possible, considering the availability and objectives of “enhanced publication” options and open access to increase reach, comprehension, and impact. PRO publications must be written in a clear and engaging way, explaining the instrument in simple terms, and addressing the “so what?” question – ideally with an accompanying plain language summary. And PRO publications must *always* thank the patients.

The basic principles of publication planning are simple: to deliver the right data to the right audience at the right time. From a pharmaceutical company perspective, publication planning has traditionally focused on the clinical study programme; because pharma companies are required to register the clinical studies they conduct and to disseminate the results in a timely fashion,<sup>1,2</sup> effective publication planning aims to publish data as soon as needed, with the greatest possible impact. Key considerations have therefore been “who” (authorship), “when” (timing), and “where” (journal/conference selection).

But while these principles still apply, publication planning has evolved to address ongoing changes in the landscape of healthcare decision makers, and their different demands for data. This article summarises why publications on patient-reported outcomes (PROs) are an essential element to demonstrate the value of a health intervention, and how PRO publications can be planned optimally, giving guidance on best practices for communicating PRO data effectively.

### Why publications on PROs are essential to demonstrating value

Pharma publications teams previously focused on the clinical development programme, with publications of “other” studies – for example health economics, epidemiology, outcomes research, real-world evidence (RWE), and PROs – typically being left to the respective

individual functions to develop. However, healthcare decision-making now involves a range of stakeholders – including physicians, payers, patients, and policy makers – each of whom has different definitions of value. Publication planning must therefore go beyond the clinical benefits of a health intervention, utilising all the available evidence to demonstrate fully its value from an economic, social, behavioural, and policy perspective.<sup>3</sup>

PROs can provide direct insights into clinical outcomes in many conditions, but also offer particular insights into the impact of a disease and potential treatments on patients and caregivers from a social perspective (e.g. humanistic outcomes, such as quality of life and daily functioning), and from a behavioural perspective (e.g. individual and emotional drivers, such as perception of benefit/risk, treatment experience, and adherence).

In many ways, PROs represent the ultimate in “real-world” outcomes – and yet the drive towards RWE and “Big Data” has increased the application of routinely collected data from healthcare databases, which often do not include assessments of PROs or the patient voice at all. In addition, patients and caregivers are increasingly accessing specialist literature directly – which brings opportunities to reach these key audiences, but also challenges in ensuring comprehension. It is therefore as

important now as it has ever been to include PRO studies in publication planning.

### Understanding the range of publication opportunities for PROs

PRO studies offer much more scope for publication than simply reporting the PRO endpoints of a clinical trial in the primary article. Development of a new PRO instrument – or validation and application of an existing PRO instrument in a new indication or patient population – offers a wide range of publication opportunities that are not always recognised in publication planning (Table 1).

It is common practice early in the development process, when planning for the inclusion of PROs in a clinical study programme, to conduct a systematic literature review of the use of PRO instruments in the indication/patient population of interest. Such reviews have traditionally been considered internal fact-finding and have not been published, but actually provide essential “due diligence” to support

the choice of PRO instrument for subsequent studies.<sup>4,10,11</sup> Similarly, there is increasing demand for PRO results from randomised controlled trials (RCTs) or RWE studies as standalone publications, even when the top line data have been disclosed in a primary

Publication planning must go beyond the clinical benefits of a health intervention to demonstrate its value from an economic, social, behavioural, and policy perspective.

Table 1. Development and utilisation of PRO instruments provides a wide range of publication opportunities

Identified need	Publication opportunity	Example publication
Find out what PRO instruments are already available	Systematic literature review	Vakil et al. <sup>4</sup>
Develop conceptual framework and draft PRO instrument	Patient and physician focus groups and cognitive interviews	Jones et al. <sup>5</sup>
Confirm conceptual framework and assess properties of PRO instrument	Validation study in relevant patient samples	Jones et al. <sup>6</sup>
Collect, analyse, and interpret PRO data from patients	Clinical trials incorporating PRO endpoints	Mitchell et al. <sup>7</sup>
Utilise PRO data to determine patient health state utilities	Mapping study of PRO instrument to generic HRQoL/utility measure	Kay et al. <sup>8</sup>
Modify PRO measure for wider usage	Cultural adaptations, translations, evaluations in related diseases	Hongo et al. <sup>9</sup>

Abbreviations: HRQoL, health-related quality of life; PRO, patient-reported outcome.

publication.<sup>12–14</sup> Qualitative data (such as thematic interviews), preference studies, and surveys of patients and caregivers are also often overlooked as a potential source of publications – yet such studies provide important context to the impact of a disease and its treatment on patients and caregivers, and are also increasingly in demand from mainstream peer-reviewed journals.<sup>15–20</sup>

## Guidance on publication planning for PROs

### 1. Identifying which PRO data can be published

A key first step in publication planning for PROs is to assess what studies will be performed, and to consider the publication opportunities that these provide. Table 1 provides a brief overview of different types of publication that can be developed from PRO studies, and here it is essential to take into account the perspective of the target audiences. For example, if the PRO instrument(s) being used have been newly developed, or are being used for the first time in a new indication, then the publication plan will need to include articles that introduce the PROs to the audience and provide the context that explains why they were developed and how they work. Conversely, if the PRO instrument is already well established in the disease area, then it may be more appropriate to plan articles that review previous publications of PRO data in that indication, to provide context for the new studies that are to come.

The process for identifying potential PRO publications starts with close review of clinical trial protocols (which should ideally have PRO endpoints described in line with SPIRIT-PRO guidelines)<sup>21</sup> to identify what PRO data will ultimately come from RCTs – because the publication plan should aim to “set the scene” and provide appropriate context for these results. The next step is to review plans for specific patient outcome studies led by other internal functions; these vary from company to company, but typically include a specialist PRO or Patient Centricity/Engagement function, or come under the wider remit of Health Economics and Outcomes Research (HEOR). Taking a collaborative, cross-functional approach to publication planning is particularly important for PRO data, in order to coordinate efforts and avoid communications being developed in inconsistent and siloed fashion.

### 2. Engaging with the right authors

A publication on PRO data from a multi-centre clinical trial will typically be authored by members of the writing committee for that study, alongside relevant representatives from the sponsor company (e.g. the responsible Medical Director and Study Statistician), following the International Council of Medical Journal Editors (ICMJE) guidelines on authorship.<sup>22</sup> ICMJE guidelines also cover other types of PRO publication (such as systematic literature reviews on the use of PROs, patient-level qualitative research, validation studies), but authorship of these may be less easy to determine. PRO studies are commonly outsourced to specialist vendors, and so it is common – but not best practice – for authorship of PRO publications to be limited to relevant representatives from the vendor and the sponsor company (e.g. the HEOR or PRO lead).

#### Best practice tips – authorship

Help communicate the clinical relevance of the PRO data through:

- **involvement of clinicians as authors**, to give essential clinical perspective and validation of the practical relevance of PRO data
- **involvement of patients/caregivers as authors**, where appropriate, to provide validation that the PRO data are reflective of their individual “real life” experience.

Inclusion of clinicians and patients/caregivers as authors can be particularly effective for interview- or survey-based research.<sup>23,24</sup> Planning for clinician/patient/caregiver input at an early stage ensures that the authors can contribute fully to the study and publication, and thus meet ICMJE criteria for authorship.

### 3. Targeting the right journals and conferences

Fundamentally, the “right” journal or conference for any publication is the option that gives maximum exposure of the data to the most appropriate target audience in the timeliest fashion. Although there are a number of technical journals and conferences focused on PROs, growing interest in the patient voice among physicians, patients, payers, and other decision

makers means that such journals and conferences should not necessarily be the default choice for PRO publications, because they typically do not reach these audiences.

#### Best practice tips – journal selection

Target PRO data directly to physicians, patients, payers, and other decision makers by:

- **submitting PRO data to mainstream clinical journals and conferences**, wherever possible, and reserving technical journals and conferences for methodologic aspects
- **publishing full papers open access**, enabling interested parties to obtain the relevant full articles without having to pay for them.

The process for selecting target journals for PRO data needs to go beyond the usual parameters that are assessed in clinical study publication planning (e.g. impact factor, lead times, and geography). Careful research is required into aspects such as a journal’s receptiveness to PRO publications, their prior record of publishing different types of PRO study, and whether the editorial board includes academic expertise in PROs, to ensure meaningful peer review.

### 4. Writing up PRO studies in a clear and engaging way

Although writing the PRO publications *per se* is strictly outside the scope of publication planning, some guidance here is pertinent because even the best-laid plans will fail – that is, the journal articles or conference abstracts will be rejected – if the PRO data are not presented in a clear and engaging way. It is essential to consult reporting standards for PRO data, such as CONSORT-PRO or those developed by the International Society for Quality of Life Research (ISOQOL),<sup>25,26</sup> and guidance from learned societies such as the International Society for Pharmacoeconomics and Outcomes Research.<sup>27</sup> Following guidance from regulatory bodies (FDA and EMA) on the validation of PRO instruments is also advisable, and is particularly important if the PRO data are intended to support a label



claim. Where appropriate, qualitative studies on patient experience and outcomes should be written in line with relevant general standards such as SRQR (Standard for Reporting Qualitative Research) and using specific standards for individual methodologies, for example COREQ (COnsolidated criteria for REporting Qualitative research) for interviews and focus groups.<sup>28,29</sup> Beyond these frameworks, there are several simple steps that can be taken to make PRO data easier to understand for a non-specialist.

### Best practice tips – writing PRO publications in a clear and engaging way

- **Explain technical terms or jargon when they are first introduced.**
  - Ideally one simple sentence, with a glossary if appropriate.
- **Outline briefly how the PRO instrument works.**
  - How and when is it administered, and to whom? What domains are included? How are they scored? What is normal vs mild/moderate/severe disease? Is improvement an increase or decrease in the score?
- **Address the “so what” question.**
  - How do changes in PRO scores relate to meaningful functional improvements? Do threshold/subgroup analyses express the data more usefully than group means? What is the clinically important difference?
- **Apply measures of readability to the publication.**
  - The Flesch or Flesch-Kincaid scoring system can be helpful, as can metrics such as the average number of words per sentence and the average number of syllables per word.

### 5. Going beyond the publication

As with all highly technical disciplines, publications on PRO data benefit greatly from supplementary information – or “enhanced publication options” – that can help non-specialists understand the results. Going beyond the conference presentation or journal article is therefore essential for PRO data.

### Best practice tips – enhanced publication options

Select publication enhancements according to the objectives that they can achieve:

- **enhance comprehension**, support with education-focused additional materials and formats (e.g. plain language summary, explanatory videos)
- **increase reach**, engage available channels (e.g. media, email, health-care practitioner (HCP) community communications, and social sharing as appropriate)
- **drive real-world clinical impact**, translate the evidence into action with tools (e.g. apps, decision algorithms).

For PRO publications, the primary concern is generally to enhance comprehension; PROs are poorly understood and their application to clinical practice is often unclear. Increasing reach is important if the initial publication is unlikely to be read by all intended audiences (e.g. an article in a technical PRO journal will not be read by clinicians). Driving impact may be a consideration where there is potential for enhancing clinical adoption of a PRO instrument.

The most obvious supplementary element for a PRO publication is the plain language summary (PLS – an acronym that is also used for “patient lay summary”). Although EMA guidelines require a PLS to be posted for all clinical studies<sup>30</sup> – and this may include PRO data – the EMA PLS template is not particularly suited to explaining the technical and methodologic aspects of PRO studies. Given that regulatory guidelines do not mandate a PLS for other types of PRO study, it is recommended that a PRO publication is accompanied by a specifically tailored PLS that describes the study in a clear and engaging manner, covering the issues noted in the previous section. For journal articles, a PLS can often be provided as a peer-reviewed supplementary document associated with the article.

Other explanatory materials to accompany a publication could include an infographic

summary, author video, animation, interactive annotated publication, and glossary of terminology, to name just a few examples. In addition to helping explain the study and aid understanding of its outcomes, these can provide a powerful stimulus to social sharing, and thereby help communicate to audiences who may not access the original publication. For journal articles, these should ideally be peer-reviewed supplementary materials associated with the article. For conference presentations, a number of options (including augmented reality, which provides a link from physical materials to embedded digital content) can enable access to these supplementary materials.

To maximise effectiveness, choice of the type of material should not only be guided by the tactical objectives (comprehension, reach, or impact) but also closely integrated with wider medical affairs communication planning. In all cases, compliance with relevant regulatory and promotional guidelines on the dissemination of data is of course essential, but is rarely prohibitive. With respect to the patient perspective, a good example of enhanced publication elements (summary slides and author video)<sup>31</sup> accompanies an article reporting qualitative research on patient and physician perspectives in multiple sclerosis.<sup>23,24</sup>

### Never, ever forget ...

... that any publication of any study involving patients, should thank patients for their contribution. A short statement in the Acknowledgements section of a conference presentation or journal article is simple to do, but will be hugely valued.

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Professionals and The International Publication Planning Association.

Going beyond the conference presentation or journal article is essential for PRO data.

## Conflicts of interest

The author is employed by, and is a shareholder of, Oxford PharmaGenesis, a HealthScience communications consultancy that provides services to pharmaceutical, medical device, nutraceutical, and diagnostic companies.

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# Patient-reported outcome measure translation: An overview

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## Abstract

The unique nature of patient-reported outcome (PRO) measures presents unique challenges for translation. Regulators emphasise the importance of maintaining conceptual equivalence across all languages in multilingual and multinational trials, while making necessary cultural adaptations. This article will provide an overview of the central issues affecting PRO measure translation, best practices for PRO measure translation, and ways to improve the translatability of PRO measures at the development stage.

be written in non-technical language to ensure they are understood by diverse populations of laypeople (including those with low levels of education and literacy) and must be interpreted consistently enough to provide meaningful data. The need for translation in multilingual and multinational trials only compounds these challenges, as the concepts being measured (often subjective) must be rendered in ways that are both understandable to each local population

(itself diverse) and consistent across all languages in the trial.

The translation of PRO measures thus proceeds differently from that of other clinical outcomes assessments in order to achieve this delicate balance of cultural adaptation and conceptual equivalence. In the following article, we will provide an overview of the translation process for PRO measures and its regulatory basis, as well as reflections on the difficulties most commonly encountered while translating PRO

measures and how those difficulties can be mitigated by considering translatability during PRO measure development.

## Regulatory guidance and industry standards

### EMA and FDA guidance

Translation and cultural adaptation of PRO measures are addressed by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), as they affect data collection for primary and secondary endpoints.<sup>1,2</sup> Both bodies indicate the importance of evaluating the process used in translating PRO measures in order to assess whether content

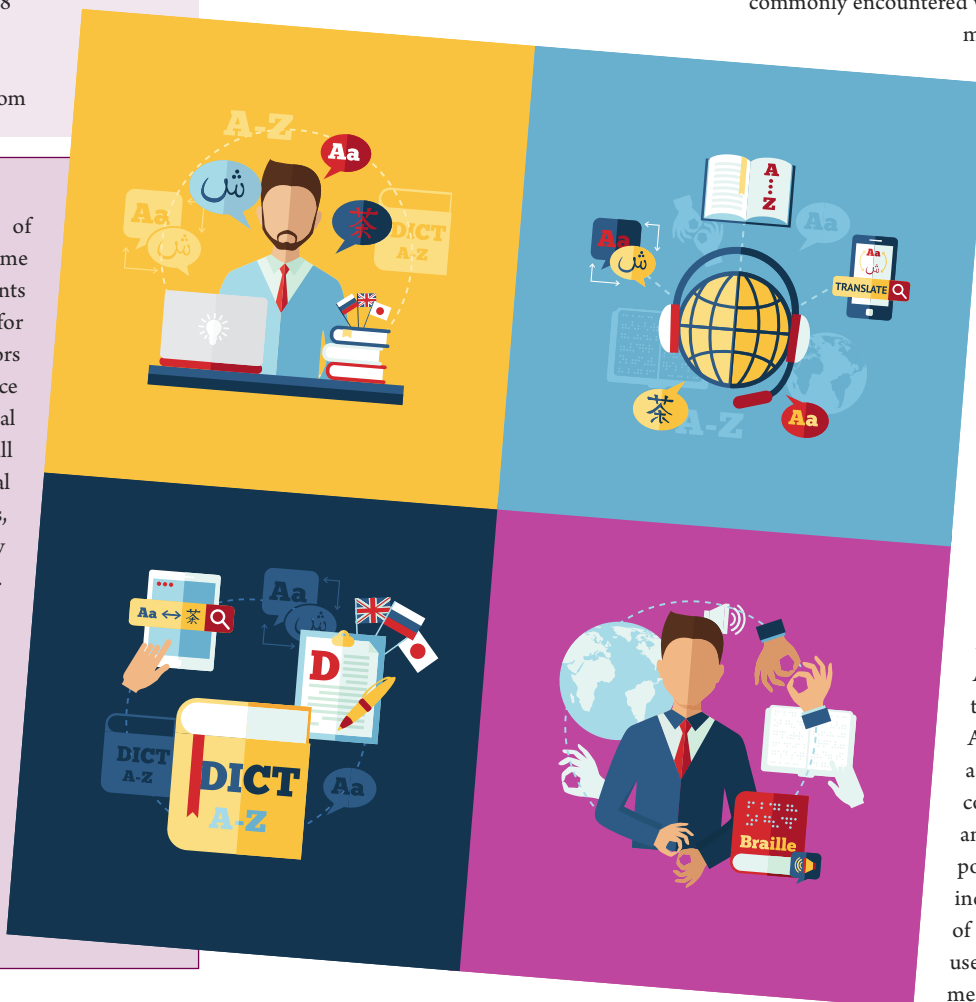
validity has been maintained across all languages in a trial. However, neither body provides detailed requirements or guidelines for the process to be used.

### ISPOR and ISOQOL guidelines

In lieu of detailed regulatory guidance, industry

The translation of PRO measures must achieve a balance of cultural adaptation and conceptual equivalence.

Patient-reported outcome (PRO) measures make unique contributions to clinical research. By asking patients to report their own experiences directly, PRO measures allow researchers to evaluate effects on patients' quality of life in ways that reporting by healthcare professionals simply cannot. But this unique role entails unique challenges. PRO measures must



standards for translating PRO measures have been shaped by two non-regulatory organisations. In 2005, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Taskforce for Translation and Cultural Adaptation released a report outlining best practices for PRO measure translation.<sup>3</sup> This was echoed in 2013 when the International Society for Quality of Life Research (ISOQOL) published recommended minimum standards for PRO measures.<sup>4</sup> The full process outlined in the following section, commonly referred to as linguistic validation (LV), reflects the best practices detailed by ISPOR.

Both the ISPOR and ISOQOL recommendations emphasise the need to verify quality through qualitative assessment, most likely through cognitive interviewing or debriefing. In cognitive debriefing, each translation is tested with patients from the target population (or alternately with laypeople) who are interviewed to confirm that the translation is clearly understood, accurately interpreted, and perceived to be culturally relevant. Best practices in the industry thus dictate that feedback from the target audience of translated PRO measures be employed to validate the quality of the translations.

## Overview of the full linguistic validation process

The full LV process through which translations of PRO measures are developed includes a number of safeguards to ensure conceptual accuracy and equivalence, as well as cultural relevance. Different questionnaire developers and translation companies employ slightly different processes, which can be considered variations on the model below:

1. Explanation of concepts: A document is developed by the questionnaire's developer or the translation company, during or after the development of the PRO measure, to clarify the intended meaning of the key concepts in the source text of the questionnaire. The explanation of concepts serves as a reference for translators throughout the LV process to guide their interpretation of the source text when rendering it in the target language.
2. Forward translation and reconciliation: Two translators independently translate the source text, then collaborate to reconcile their translations and create a single forward



translation. This reconciliation process serves as a check on each translator's interpretation of the source text, selecting for a more accurate and appropriate translation.

3. Back translation and review: A third, independent translator then back-translates the reconciled forward translation to English (or other source language). The back translation is compared to the source text to identify discrepancies in the rendering of key concepts. Any discrepancies are resolved through discussions with the team of translators, revision of the forward translation, and back translation of the revised wording.
4. International harmonisation: Back translations from all languages in the scope of the trial or translation project are reviewed together to identify conceptual discrepancies across languages and verify a coherent approach to rendering concepts. Where problematic concepts are identified, further guidance may be sought from the questionnaire's developer.
5. Expert reviews: Draft translations may be reviewed by experts in the target countries (e.g. clinicians, client subsidiaries, developer subsidiaries) to ensure that the translation aligns with local usage.
6. Cognitive debriefing: Interviewers in the target countries test the draft translations with diverse subject populations of laypeople or patients, identifying concepts that are not accurately understood or that are perceived not to be culturally relevant. Through discussion with the team of translators, and in view of problems identified in other languages, highly problematic concepts may

be revised through a process similar to the one described in #3.

7. Proofreading: The final product is proofread by a translator to ensure it is free of errors.

## Key concerns in translating PRO measures

As reflected in the process outlined above, PRO measure translation differs from other forms of medical translation in fundamental ways. PRO measures must achieve conceptual validity using nontechnical language, and must do so consistently across languages. Translators of PRO measures must carefully assess the best ways to reflect the content and register of an everyday expression using what may be a very different set of everyday expressions in another language. For this reason, translation of PRO measures reflects a distinct area of expertise within the field of medical translation. Both the LV process described above and the specific competencies of the translators involved contribute to achieving quality PRO measure translations.

### Allowing cultural adaptation

The task of cultural adaptation during the PRO measure translation process falls first to the forward translators. While creating their initial translations and a single reconciled translation, the forward translators must consider which concepts in the source text of the questionnaire can be translated literally without loss of meaning, and which must be adapted to suit the cultural context of the target language. Such adaptations can range from using different linguistic structures or idiomatic expressions with similar meaning to providing entirely different examples (e.g. culturally adapted examples of sports or food). Whatever the scale of the adaptation, translators must consider how to increase cultural relevance in a way that maintains the integrity of the concept being measured.<sup>5</sup>

The effectiveness of the forward translators' cultural adaptation is assessed during cognitive debriefing, wherein subjects in the target country may provide feedback about the translation's cultural relevance and offer suggestions for better adapting the translation.

### Ensuring conceptual equivalence

Of course, cultural adaptation of PRO measures cannot be pursued at the expense of maintaining

conceptual validity across all languages in the trial. The LV process thus includes a number of safeguards to ensure that translations are not inaccurate (either due to translators' misinterpretation or by over-adaptation).

The first of these safeguards is the explanation of concepts, which prevents inaccuracies by providing the translators with a clear definition of each item at every stage of the process.

Back translation review allows for conceptual equivalence to be directly assessed. Conceptual discrepancies that are identified during back translation review may be easily resolved if they reflect a misinterpretation of the concepts in the source text, or they may require further discussion with the team of translators to determine what translation best reflects the source concepts without unduly sacrificing cultural relevance.

Here again, cognitive debriefing can evaluate the success of the negotiations between adaptation and equivalence, and help make revisions to the text where needed.

## Developing PRO measures with translatability in mind

Though the LV process and the expertise of PRO measure translators ensure a quality translation, the translatability of the source text of the questionnaire fundamentally affects how well it can be rendered in other languages. The clarity and discreteness of the concepts being measured in the source text directly impact the degree to which strict conceptual equivalence is possible across languages.

When developing PRO measures, avoiding two common pitfalls can greatly increase the translatability of the questionnaire.

### Pitfall #1: Semantically rich concepts

Many concepts of interest to quality of life research, and so commonly assessed by PRO measures, are compound, describing many symptoms and experiences. Such concepts may already be ambiguous in the source text, and subjects may place emphasis on different aspects of the concept and therefore interpret the item differently. The ambiguity is only amplified in translation, since the symptoms and experiences that make up the compound concept may be grouped differently in other languages and it may therefore be difficult to articulate the same complexity without introducing concepts,



eliminating elements, or shifting emphasis. For these reasons, compound concepts such as *fatigue*,<sup>6</sup> *bother*,<sup>7</sup> *frustration*,<sup>8</sup> and *distress*<sup>9</sup> should be avoided where possible.

### Pitfall #2: Overlapping concepts

Response sets are integral to the data-collection function of PRO measures but can present a particular challenge for translation.<sup>10</sup> Gradations of amount or degree are distinguished differently from language to language, making it difficult to maintain the differences between response options without departing from the concepts in the source text. It is therefore preferable to use distinct concepts where possible, rather than gradations of amount or degree. For example, the response set “None of the time / A little of the time / Some of the time / A lot of the time / Most of the time / All of the time” should be replaced by “Not at all / Rarely / Sometimes / Often / Always”. Where using distinct concepts is not possible, the shift to a numeric rating scale can allow for replacing potentially overlapping concepts of amount or degree with clearly differentiated numerical responses.

### Tools for improving translatability

To assess the translatability of PRO measures at the development stage and to identify items that will benefit from revision, it is recommended that PRO measures undergo the processes of face validation and/or translatability assessment.<sup>11–13</sup> In face validation, an expert reviews the questionnaire to ensure that all concepts are clear, discrete, and unambiguous, while in translatability assessment, translators review the questionnaire to identify areas of potential difficulty for translation. Items identified as problematic by either process can then be

referred back to the questionnaire's developer for revision.

Attending to PRO measure translatability at the development stage creates source texts that contain less ambiguity and fewer culturally-specific concepts, making it easier to maintain consistency and make appropriate cultural adaptations during the translation process. This up-front investment leads to fewer delays during the translation process and higher quality data in the trial.

## Conflicts of interest

The authors declare no conflicts of interest.

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## My experience attending EMWA conferences



To my surprise, the people at the EMWA conference were really friendly and welcoming. They were coming to me after seeing my green badge, introducing themselves, and insisting that I not be shy.

It all started few years ago in a “career day event” organised by my previous postgraduate programme. I knew nothing about medical writing, let alone EMWA. Among several speakers, who were describing different job opportunities with various responsibilities and roles, it was the lecture about medical writing that made me the most curious. I knew I liked science and I liked writing, specifically scientific writing, so “medical writing” stuck in my head. About a year later, I applied for a medical writing job, although the agency apparently needed an experienced writer. I did not get the job, but still, the idea stuck in my head.

After that, while I had started a new postdoctoral position, I decided that I still would like to know more about medical writing. Although I was a bit sceptical and, to be honest, scared, I registered for EMWA’s conference and signed up for a couple of workshops. To my surprise, the people at the EMWA conference were really friendly and welcoming. They were coming to me after seeing my green badge, introducing themselves, and insisting that I not be shy. They explained what they did and how they ended up in medical writing. This happened throughout the conference – from the first networking event to the coffee breaks between workshops, at the breakfast tables, and of course during the social events. All of this made me feel comfortable during the conference. Moreover, the workshops with their precise pre-workshop assignments and well-organised lectures convinced me that it was the right decision to register for this EMWA conference and that I should register for forthcoming conferences. The various workshop topics, from regulatory writing to proofreading techniques, and even writing for the internet, make it possible for almost everyone to have choices and benefit even without any previous knowledge.

Though I still do not know where my career will take me, for someone who works most of the time in the laboratory, attending EMWA conferences, symposia, and workshops is a valuable investment and experience. Needless to say, meeting old friends and finding new ones is also a pleasant part of it.

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# Systematic hospital collection of patient-reported outcome data via patient apps

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## Abstract

Medical writers are increasingly likely to come across patient apps in their work, and we describe here the background and use of two apps for assessing patient-reported outcome (PRO).

Systematic collection of PRO data via patient apps has been recently introduced in a large Danish university hospital. Experiences so far show that the approach can help staff to focus on the individual patient's needs and can improve communication between patients and staff. Some patients have also been able to avoid unnecessary hospital visits.

Effective clinical use of systematic PRO data requires the data to be easily accessed and visualised, and both patients and staff need to know that the data provided will make a meaningful contribution to health care.

Patient-reported outcome (PRO) measures have been used for some time in the Danish healthcare sector, with patients completing questionnaires about their health and treatment experiences. This has mostly occurred through research projects, and questionnaires have traditionally been in paper form and sent through the post or completed at the clinic. The last few years have seen major changes, however, primarily in the way the questionnaires are completed, the breadth of PRO use, and the ambition

level for using the data that are collected.

This change in PRO use is partly a result of developments in the Danish Healthcare Quality Programme that was introduced in 2004.<sup>1</sup> This programme aims to ensure continuous development of the quality of care to create better patient pathways and to prevent errors and unintended events in the healthcare system. Two fundamental objectives of the programme are to involve the users – patients and their relatives – in healthcare decisions and to ensure a patient-centred culture within hospital departments.



A main strategy in the 2015 to 2018 national quality programme is to work towards the systematic use of cross-sector PRO measures with the aim of directly influencing treatment decisions and ensuring quality of care.<sup>2</sup> Such PRO data should include patient-reported symptoms, self-assessed health, and treatment experiences and should enable assessment of the effect of a treatment or health intervention.

This means that it will be essential to collect valid, reliable data to guide decision-making and the development and evaluation of health services. The systematic use of PRO data is generally seen as a positive step, but it is still a developing concept, and as yet there is no national consensus on which PRO measures should be used and in what format.

### Systematic PRO data as a priority at OUH – Svendborg Hospital

Odense University Hospital (OUH) and Svendborg Hospital together provide local and acute services for the Danish island of Funen. They represent the largest referral hospital in Southern Denmark, with all medical specialties, approximately 1,000 hospital beds, and about

1 million outpatient visits per year (data from OUH management). In addition, OUH takes patients from all over Denmark due to its highly specialised services.

OUH and Svendborg Hospital have prioritised the systematic collection of PRO data in the expectation that this will benefit patients – primarily through faster and more appropriate diagnostic pathways and fewer, more targeted follow-up visits. PRO data have been key aspects of clinical research for some time, for example the collection of EQ-5D data alongside measures of functional independence and physical mobility for patients undergoing orthopaedic surgery,<sup>3</sup> the development of a quality of life questionnaire for thyroid disease,<sup>4</sup> and quality of life in toddlers with middle ear disease.<sup>5</sup> Systematic collection of PRO data is not without its challenges, however, including lower completion rates for elderly patients with impaired cognitive skills,<sup>3</sup> and the need to reassure healthcare staff that the PRO data make a meaningful contribution to the individual patient’s care.<sup>6</sup>

OUH has recently established a networking group for departments using PRO measures on a systematic basis. This means that departments can help each other and can draw from each other’s experiences using PRO measures. “The

departments are very positive. Most of them use PRO measures that have already been developed, which is of course the easiest solution. Others will have to develop new measures, and that is a challenge. But they can take advantage of the experiences we already have and can use the existing PRO measures as a starting point”, says Jon Sigurjónsson, PRO consultant at OUH.

The availability of electronic platforms has significantly changed PRO data collection. Instead of developing paper-based PRO questionnaires for a single purpose and then discarding them after the requisite number of years, the data can now be collected via platforms such as RedCap or apps on mobile devices that facilitate storage, analysis, and feedback.<sup>7</sup> Many of the PRO measures that will be used for systematic data collection at OUH will be implemented through the regional app, “My Patient Journey”.

### My Patient Journey – an app for patients and medical staff

The “My Patient Journey” app was developed in 2014 at the Centre for Innovative Medical Technology at OUH for easier digital communication between patients, medical staff, and hospital departments.<sup>8</sup> The app helps patients find and keep track of information from the hospital and aims to give them a better overview and experience in communicating with the hospital. Today, it is in use all over the Region of Southern Denmark by approximately 44,000 patients and 2,000 clinicians (data extracted from “My Patient Journey”). The app is primarily for patients, but it can be downloaded from Google Play or App Store (as “Mit forløb”).

The “My Patient Journey” app is now the user interface for patients at OUH. Patients can send text messages to medical staff and can access information about their own treatment in the form of text, videos, and images (thus replacing

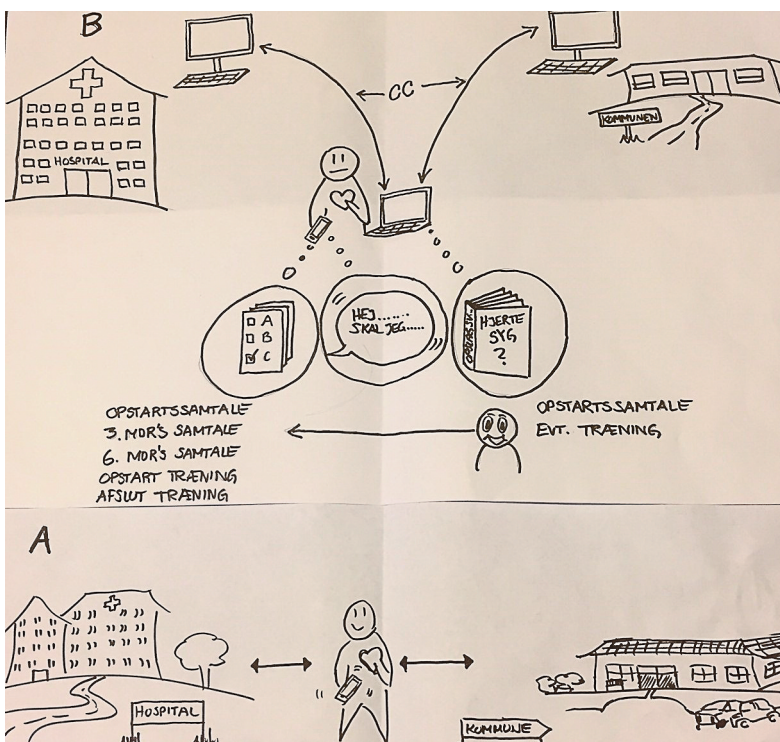


Figure 1: Comparison of the old and the new follow-up systems for patients who have undergone a cardiology intervention

A (lower picture): the ‘old’ - the patient visits the hospital and the municipal rehabilitation service in person. B (upper picture): the ‘new’ - the patient sends health status data to the hospital and the municipal rehabilitation service, who then advise on the form and frequency of follow-up.

the more general paper pamphlets). The app is also a platform for the patients to enter data – such as weight or blood pressure – and for answering questionnaires uploaded by the medical staff.

The nursing staff are the main operators of the app in the hospital. The app has been integrated into the electronic medical journal that is already used on a daily basis for recording patients' visits and information and for exchanging data with other hospital departments, general practitioners, and the municipalities.

The "My Patient Journey" app can be adapted to the specific needs of the hospital department and for selected patient groups. Clinical departments are thus free to choose which PRO measures and other questions should be included. This is typically done with patient involvement to ensure relevant data collection and minimal respondent burden. The emphasis for PRO measures is on existing, validated health and quality of life questionnaires.

When questionnaires are applied within the "My Patient Journey" app, an algorithm can be created that calculates a score based on the individual patient's answers. The patient's score can then determine how the medical staff should follow up with the patient.

## A PRO app for patients in a heart rehabilitation programme

The cardiology clinic at Svendborg Hospital has been running a pilot PRO project in a partnership with the municipal rehabilitation services. This is a cross-sector collaboration where the responses that patients make to the medical staff's questions and to the PRO measures are made available to the hospital department and the municipal rehabilitation services at the same time (Figure 1).

The two PRO measures used in this project are the Hospital Anxiety and Depression Scale (HADS) and the HeartQoL. Both have 14 items; the HADS can be used to identify persons at risk of clinical anxiety or depression, while the HeartQoL was developed by the European Association of Preventive Cardiology for patients with ischaemic heart disease. The department has been collecting patient data using these PRO measures for some time, but in paper form.

In this project, the PRO measures are loaded

into the "My Patient Journey" app, and patients who have undergone a cardiology intervention are asked to complete them at the first nurse consultation (about two weeks after the intervention) and again after three and six months. In the meantime, the patient is referred to a rehabilitation programme including exercise training and education on healthy living with heart disease.

The objective of the project is to see whether the PRO data can enrich the patients' contacts with the hospital and municipal services through more relevant discussions and treatment. This may be in the form of a more individualised rehabilitation programme or interventions for anxiety, depression, cessation of smoking, weight loss, etc.

The 30 patients who have participated in the project so far have given positive feedback. They like the easy interactive format where they can just send an SMS to the nurse they know to ask about something in their daily life, and they know that the nurse's answer is based on the patient's current health and status. They also feel better prepared to talk to the nurse at their next consultation and to discuss health and emotional issues.

The nurses have found it easier to prepare for consultations with patients and can focus the discussion on the issues that the individual patient is currently facing. The PRO data enable the staff to stratify patients earlier on, and patients who are doing well and do not need close follow-up can avoid unnecessary hospital visits. The advantages for the rehabilitation staff are that the patient-reported data on problems and challenges help them to better plan the rehabilitation programme in advance, provide a way of following the patient's progress, and can identify areas that need more focus.

An issue still requiring attention is the response rate to the PRO measures completed via an app, as some patients were less accepting of this approach. These were especially older patients who were less familiar with smartphones and tablets. This will be one of the aspects to be evaluated during the next phase of the project,

which is introducing the PRO app into routine clinical use.

## A PRO app for patients undergoing prostate cancer surgery

Following a successful two-year project,<sup>9</sup> a PRO app is now used routinely with patients undergoing prostate cancer surgery at the urological ward at OUH. Using "My Patient Journey" as a platform, patients answer the questions electronically from home both before surgery and again at 3, 6, and 12 months after surgery. The questionnaire has been developed by a national working group under the Danish Health Authority and is aimed at all patients with prostate cancer regardless of the type of treatment they get. At the same time-points, the patient also has a blood test taken by the general practitioner. The PRO app scores the patient's answers, and the resulting score and blood test results give a colour-coding for whether telephone or outpatient follow-up is necessary (orange or red) or not necessary (green), see the example in Figure 2 overleaf. The objective here is to use the PRO data to reduce the number of unnecessary hospital visits.

This approach has been a great success. The use of the PRO data has eliminated two-thirds of the follow-up visits in this patient group, thus giving the staff more time for patients with more complicated problems and reducing the waiting lists.

The patients report that the app helps them to be more active and involved in their treatment and discussions with hospital staff. The app approach appears to be especially beneficial for elderly patients, who can now send a picture or a video via "My Patient Journey" instead of having to make the trip to the hospital. An important element, however, is that patients can see that the medical staff have made active use

of the PRO data, and that the data are not just collected and then stored.

Next steps include broadening the use of the PRO app, for example to patients with prostate cancer who are being treated with medicines

Effective clinical use of systematic PRO data requires the data to be easily accessed and visualised at the clinical contact, and both patients and staff need to know that the data provided will make a meaningful contribution to improved health care.

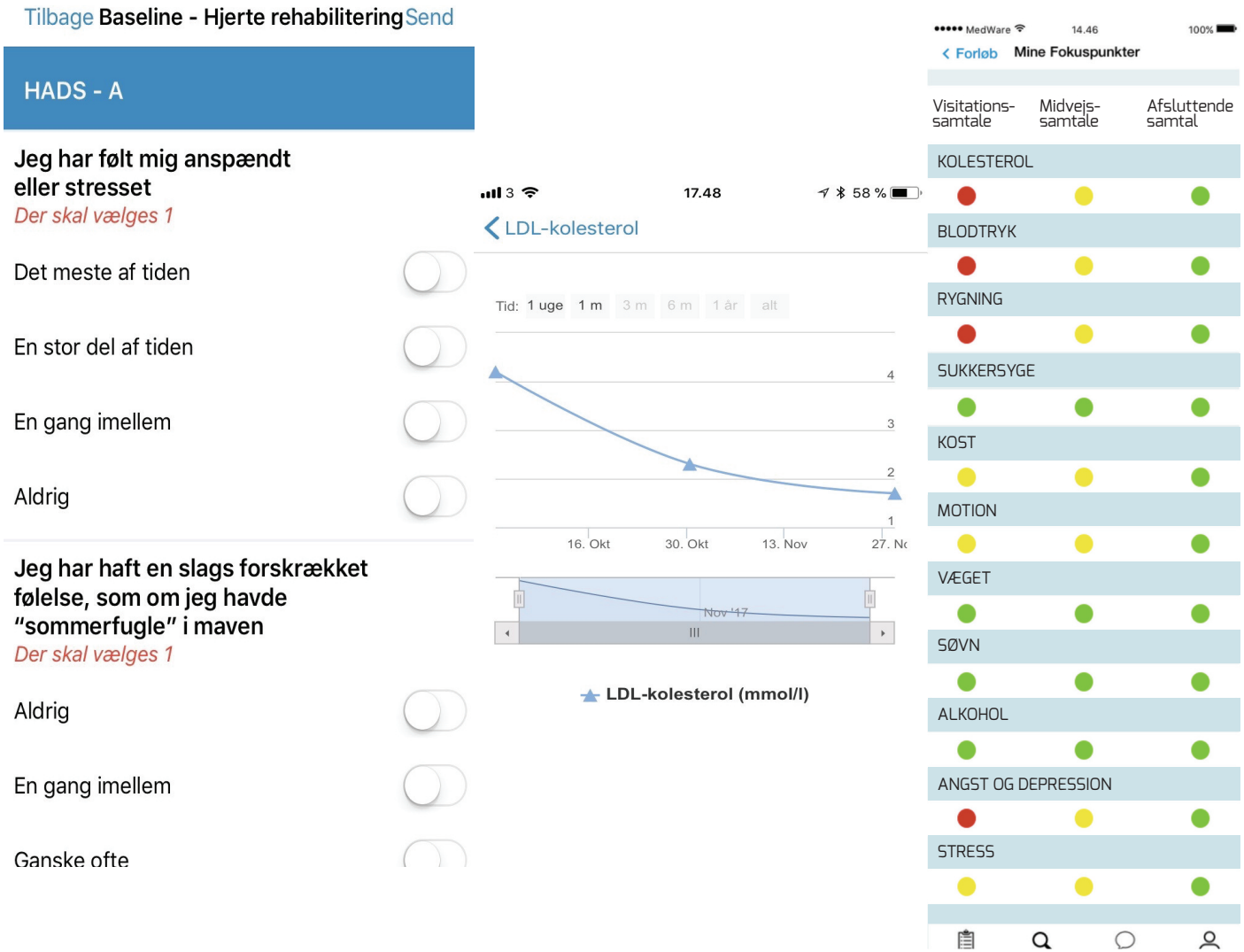


Figure 2: An example from the cardiology project of how PRO app data can be used

Here, questions from the Hospital Anxiety and Depression Scale (HADS) are combined with blood test results (here on cholesterol level) to stratify patients at follow-up to RED (current problem, needs immediate attention), YELLOW (current problem, needs follow-up), or GREEN (no current problem). In this example, the patient has several “red” and “yellow” issues at the first visit, and these improve to green over time.

English translation:

**Baseline** – Heart rehabilitation: HADS questions (Choose 1 answer): *I feel tense or “wound up”*: Most of the time / A lot of the time / From time to time, occasionally / Not at all. *I get a sort of frightened feeling like ‘butterflies’ in the stomach*: Not at all / Occasionally / Quite Often / Very Often

**My focus points** [for] Initial – Midway – Final Consultation: Cholesterol – Blood pressure – Smoking – Diabetes – Diet – Exercise – Weight – Sleep – Alcohol – Anxiety and depression - Stress

rather than surgery. This may be more challenging in terms of resources, as the PRO app is not expected to reduce visits and it takes time for the medical staff to go through the patient’s answers to the questionnaire and discuss them as appropriate.

### PRO measures are the future

“It is not a question of whether or not we should use PRO measures. We should definitely use

them and much more than today – in every department in the hospital”, says Kim Brixen, medical director at OUH. “It provides possibilities for better and faster diagnostics in addition to fewer and better follow-ups. PRO measures are also useful for collecting research data, which is especially valuable for a university hospital. Depending on the patient’s diagnosis, I believe that many outpatient visits can be replaced by PRO surveys.”

Another potential advantage of the app approach to PRO data collection is in clinical research projects, where patients with baseline PRO data can easily be block-randomised and divided into intervention and control groups.

There are notes of caution when using PRO apps, however. One is the tendency to focus on the specific health issues that emerge from the patient data, thus potentially missing important information that is not asked about. A similar

problem can arise with telephone and e-mail consultations and from telemedicine, as the full picture of a person's health is only achieved through a (well-performed) traditional consultation. This is an issue that requires further research, as it could have negative effects on patient treatment.

A further issue is the extent to which the PRO measures should be piloted and validated before the hospital initiates large projects or implements routine data collection. In many countries, PRO questionnaires are typically put through a long testing process before they are used. OUH has decided to test the use of PRO measures in “real life”, however, by putting them into use and correcting any errors as they are identified.

While Denmark is known for its comprehensive system of health registers that can be linked through the individual personal identifier, it is recognised that the sharing of PRO data between patient and medical staff, and between hospital sectors, has to be done with care and attention to individual privacy. Written informed consent to share the PRO data is typically done through the PRO app. The patient is presented with relevant information, and this needs to be registered in the app as “read” before it is possible to give consent. Consent can also be withdrawn through the app. The issues surrounding data privacy and informed consent may become more prominent as the sharing of personal health data becomes more widespread.

## Conclusions

There is still much to learn about the systematic collection of patient-reported outcome data via apps as an aid to optimising healthcare treatment and care. However, it appears to be a promising approach for focusing on the individual patient's needs and current status and for improving communication between patients and healthcare staff.

An important next step is the more formal evaluation of the PRO app projects. The cardiology project described here is currently being evaluated using the Model for Assessment of Telemedicine approach. This involves assessment of several aspects such as the clinical effects, patient safety, the patients' perspectives and experiences, financial aspects, and organisational effects.

Effective clinical use of systematic PRO data requires the data to be easily accessed and

visualised at the clinical contact, and both patients and staff need to know that the data provided will make a meaningful contribution to improved health care.

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## Conflicts of interest

The authors declare no conflicts of interest.

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# The PROMIS of electronic patient-reported outcomes

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## Abstract

Paper-based questionnaires are in widespread use for patient-reported outcomes, but they can be an inefficient way of collecting patient data. Electronic patient-reported outcomes are of wide interest and have the potential to drastically change patient data collection for the better. In particular, computer-adaptive tests can reduce the question burden for everyone involved. The US National Institutes of Health has funded the development of the Patient-Reported Outcome Measurement Information System. This exciting technology is being employed in many disciplines, including orthopaedic research.

## Paper vs. electronic data collection

Most patient-reported outcome measurement tools (PROMs) were designed for paper-based collection of patient-reported outcomes (PROs). However, “question fatigue” can be a problem with this format, especially because patients are often tasked with completing more than one measure at follow-up visits to the clinic. Collecting and analysing paper questionnaires also presents logistical and cost problems to researchers.<sup>1</sup>

Electronic patient-reported outcomes (ePROs) have therefore been suggested as an improvement. A report from the International Society for Pharmacoeconomics and Outcomes Research PRO Mixed Modes Task Force stated, “Advantages of using electronic data collection include less subject burden, avoidance of secondary data entry errors, easier implementation of skip patterns, date and time stamping, reminders/alerts, edit checks, and more accurate and complete data.”<sup>2</sup> A systematic review and meta-analysis of studies conducted between 2007 and 2013 found that “PROMs administered on paper are quantitatively comparable with measures administered on an electronic device.”<sup>3</sup> However, ePROs have some potential disadvantages, including the costs associated with a custom-built

platform.<sup>4</sup> Others critique the difficulties in reaching the correct patient population. For example, can a 95-year-old patient really be tech savvy? Collecting patient data also immediately brings issues of security, privacy, and confidentiality to the fore.<sup>5</sup>

ePROs are still relatively new, and, as with all new technologies, not everyone will be an early adopter.<sup>6</sup> So, is the implementation of ePROs in a busy hospital feasible? One study examined the introduction of ePRO systems in two orthopaedic clinical practices.<sup>7</sup> Patient completion rates were 93% and 95% in the two clinics. For comparison, annual paper-based completion rates were as low as 30.6% for patients undergoing total joint arthroplasty at a single academic medical centre in San Francisco.<sup>8</sup> Thus, the authors conclude that “an electronic system to capture PRO in real time is feasible without any major disruption to the clinical work flow.”<sup>7</sup>

## Creating a powerful and validated ePRO platform

With all of these issues in mind, government-funded organisations worldwide have invested in developing standardised and usable patient-reported outcome instruments.<sup>9,10</sup> In 2004, the US National Institutes of Health began developing the comprehensive Patient-Reported



A study examining the introduction of ePRO systems in two orthopaedic clinical practices concluded, “an electronic system to capture PRO in real time is feasible without any major disruption to the clinical work flow.”<sup>7</sup>

Outcome Measurement Information System (PROMIS®).<sup>10</sup> This initiative aims to substantially improve the standards for assessing self-reported health status. Over 300 measures of physical, mental, and social health are available for use in the general population (adults and children) and individuals with chronic conditions.<sup>11</sup> The PROMIS measures have been tested and validated in large reference populations, making them suitable for research on different health conditions.<sup>12</sup>

The PROMIS initiative has generated a reliable and, oftentimes, more sensitive system than traditional PROs, customised to the patient, which poses fewer questions.<sup>13–17</sup> A systematic review of legacy patient-reported outcome measures to PROMIS in an orthopaedic setting stated that PROMIS measures “can be administered quicker and applied to a broader patient population while remaining highly reliable”.<sup>18</sup>

PROMIS utilises item response theory. In short, after the first test question (item), all following items are based on the answer to the preceding question. For example, if a person says they cannot walk 15 metres without pain, it is clear that pain interferes with their life and there is therefore no need to ask any questions related to hiking or contact sports. All subsequent questioning is meant to calibrate just how bad their pain interference is. Can they walk 5 metres without pain? Are they able to get out of bed? It is then possible to rapidly pinpoint where the patient is on the pain interference scale. Compare this method to traditional PROMs, where every question must be asked and answered in order to arrive at a final score for the patient.

PROMIS PROs can be delivered using computer-adaptive tests (CATs), which are individually tailored electronic questionnaires (Figure 1). CATs are focused on a single domain

and utilise item response theory, so the next question administered from the question bank depends on the previous answers given by the patient.<sup>4</sup> Questions continue to be posed until the patient’s score for the domain in question has been identified or the maximum number of questions has been reached. For example, the PROMIS Physical Function CAT contains a maximum of 12 questions, but typically, fewer questions are needed to identify the patient’s score – oftentimes just 5 to 7.

A common PROMIS metric enables the results of different measures to be compared and simplifies interpretation of the score.<sup>19</sup> A PROMIS score for a patient is correlated to a specific level of ability, for example, lifting a cup to your mouth or running 10 miles.<sup>14</sup>

### Clinical research and CATs

Using CATs, instead of traditional PROMs, which may contain numerous questions, may help increase patient compliance. Because a respondent’s current state of health and satisfaction is recorded quickly and precisely, surgeons can track their patients’ progress interactively and more regularly than is possible from scheduled clinical visits alone.<sup>20</sup> This may also help improve the patient’s experience and therefore patient satisfaction.

#### An example: using PROMIS CATs for orthopaedic clinical research

At Smith & Nephew, we are currently investigating using a PROMIS ePRO app in orthopaedic clinical research. If ePROs deliver on their promise, there is great potential that they

can be used in the many clinical studies that we run or fund, which can give us greater insight into how patients feel about their new medical device.

Smith & Nephew conducted a 4-month prospective cohort study to determine the usability, reliability, and validity of PROMIS CATs for patients undergoing total knee arthroplasty (TKA). In this study, TKA patients completed

PROMIS CATs on pain behaviour, pain interference, physical function, and depression pre- and post-operatively. The study also examined user experience and clinician satisfaction with the digital platform. Eighty-seven TKA patients were enrolled from five UK sites and one US site between January 2018 and April 2018. Although the results have

not yet been published, preliminary findings indicate high levels of patient engagement and satisfaction with the app, as well as high levels of completion of the PROMIS CAT surveys.<sup>21</sup> One of the clinical investigators, Professor Iain McNamara of Norfolk and Norwich University Hospitals NHS Foundation Trust (UK), speaking about the study noted: “Traditional PRO collection is time-consuming and often burdensome for both patients and healthcare professionals. Using mobile technology is a significant improvement over standard care, providing the patient with an easy-to-use tool to report their progress and enabling surgeons to track patient recovery closely. Moreover, the PRO data collection is seamless, and enables us to also evaluate our hospital’s performance”.<sup>22</sup>

### Conclusion

Only time will tell if ePROs deliver on their promise to transform clinical research but early indications are positive. One thing is certain, this is certainly not the last time that you will hear about ePROs.

### Disclaimers

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

### Conflicts of interest

The author is employed by Smith & Nephew.



Figure 1. An example question from a CAT



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## Author information

**Diarmuid De Faoite** has been a member of the EMWA Executive Committee since 2012 and is the EMWA website manager. As a result of his current position with Smith & Nephew's Global Clinical Strategy team, he has developed a keen interest in patient-reported outcomes.

# Interview with **Professor Matthias Rose** on developing patient-reported outcomes and the PROMIS initiative

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## Abstract

Professor Matthias Rose is Medical Director of the Psychosomatic Department at the Charité University Hospital in Berlin, Germany. In this interview, I discuss with him patient-reported outcomes and the Patient-Reported Outcomes Measurement Information System (PROMIS®) initiative, which, according to the PROMIS website (<http://www.healthmeasures.net/explore-measurement-systems/promis>) is “a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children” that “can be used with the general population and with individuals living with chronic conditions”.

**MEW:** Thank you for agreeing to this interview, Professor Rose. What is the most common mistake you see in the development of patient-reported outcomes (PROs)?

**Prof. Rose:** I think the most problematic thing is that people jump straight into it without thinking about what is the construct they really want to measure. Frequently, we are approached by different parties who say they want to measure “quality of life” without really understanding what is meant by that. In my view, people try to



*Professor  
Matthias Rose*

## PROMIS®

In 2004, the US National Institutes of Health initiated the development of a comprehensive Patient-Reported Outcome Measurement Information System (PROMIS®). The aim of this initiative is to improve substantially the standards for the assessment of the self-reported health status. Over 300 measures of physical, mental, and social health are available for use with the general population (adults and children) and individuals with chronic conditions. The PROMIS measures have been tested and validated in large reference populations making them suitable for research on different conditions.

The programme has generated a reliable and oftentimes more sensitive system, customised to the patient, which poses fewer questions than traditional paper-based PROMs do.

Find out more at <http://www.common-metrics.org/> or [www.healthmeasures.net/promis](http://www.healthmeasures.net/promis) where you can also take an online computer adaptive test demonstration.



bypass the first steps in developing the conceptual measurement model much too often. They pick out some established instrument from the literature without questioning its appropriateness for their particular research question.

**MEW:** Given this, how important is the development of guidelines like the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) steps in identifying and evaluating an existing PRO measure?

**Prof. Rose:** Very important. I think that the longer you are in the field, the more clearly you see the need for the basics to be correct. Initiatives like the ISPOR guidelines<sup>1</sup> are very useful in ensuring that the basic elements needed in a PRO are present.

**MEW:** Patient-reported outcome measures (PROMs) are the instruments used to measure a patient's health status or health-related quality of life at a single point in time. However, are there too many PROMs?

**Prof. Rose:** There are probably over 4,000 different PROMs out there, and most of them are carefully developed and validated. Although this is an impressive amount of work, I believe that this plethora of instruments actually hinders their acceptance. For PROMs to enjoy the same level of acceptance like biomarkers, we need much greater standardisation and less confusion.

**MEW:** Which is what the Patient-Reported Outcome Measurement Information System (PROMIS®) is trying to achieve, right?

**Prof. Rose:** Yes. Think of it like this. Today, most PROMs are like thermometers using different scales, which makes it highly complicated to compare measurement results among them, even if they measure the same construct. PROMIS provides a common metric to allow this (Figure 1). Thus, if you score your instrument on the PROMIS metric, scores resulting from different assessment tools can be instantly compared in a meaningful way. Just like using different thermometers to measure temperature.

Thus, PROMIS also addresses another old dispute in the field, which is if you favour generic or disease-specific tools. Disease-specific tools

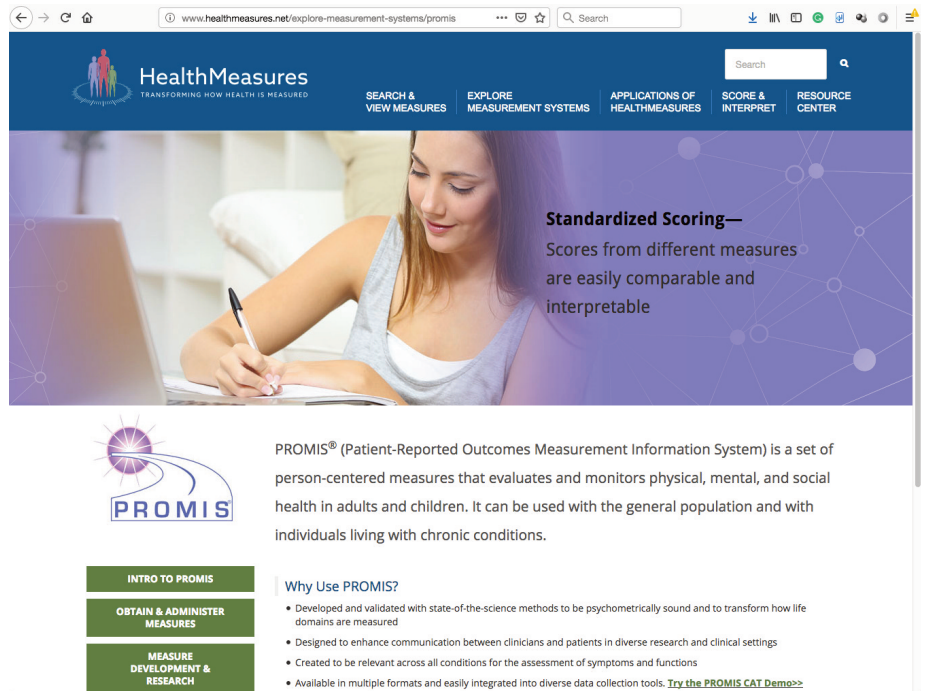
For PROMs to enjoy the same level of acceptance like biomarkers, we need much greater standardisation and less confusion.

are typically more responsive to demonstrate treatment effects, whereas generic tools allow comparisons between different clinical populations. When you look into the construction principle of disease-specific tools, essentially they are a compilation of health domains combined in one composite score.

PROMIS domains are generic, but they can at the same time act as building bricks providing a disease-specific score. Thus, the compilation of health domains is specific, not the assessment itself.

Let me give you a more concrete example. PROMIS identifies the elements such as physical function, pain, anxiety, and so on, which are relevant to everyone. You can then pick and choose the different domains which are relevant for different diseases. For example, some of the PROMIS domains are relevant for both heart disease and musculoskeletal disease (e.g. physical function), but others are only relevant for heart disease (e.g. dyspnoea).

This is the core of the idea behind PROMIS. The combination you choose is disease-specific



**Figure 1.** Home page of the PROMIS website, which is part of HealthMeasures.

HealthMeasures consists of four precise, flexible, and comprehensive measurement systems that assess physical, mental, and social health, symptoms, well-being and life satisfaction; along with sensory, motor, and cognitive function.

but not the constructs! We have liberated the different domains from being tied to specific instruments – and diseases.

**MEW:** You have been involved in PROMIS since it began and are the Chair of PROMIS Germany. You have seen a lot of progress, but what is the next quantum leap for PROMIS in your opinion?

**Prof. Rose:** PROMIS started because we had new methods like computer-adaptive tests (CATs), which could be employed for more precise measurements. In addition, the initiative has such political clout with the necessary funding behind it to make it happen. But the bigger achievement of PROMIS is that it creates a framework of health. It has the potential to set scales independent from the tools, indispensable for standardisation. Consider it this way, for the first time, in the world of patient-reported outcomes, we would have definitions and scales that are as easy to understand as, for example, the Celsius scale is for temperature.

There will never be complete agreement on which instrument to use, that's human nature. After all, people never want to have just one type of car, but the advancement in PROs that

PROMIS will bring means we are moving closer to achieving the status of biomarkers that I previously mentioned.

**MEW:** Given that you are talking to EMWA, what country in Europe is furthest in developing and adopting PROMs?

**Prof. Rose:** In my opinion, it is the Netherlands. The Dutch mindset has always been innovative and open to adoption. If you look at different research consortiums for European Union funding etc., the Dutch are always well represented. So, if I had to pick any one country in Europe, I would choose the Netherlands.

**MEW:** What should medical writers keep in mind when they write about PROs?

**Prof. Rose:** They should be careful with the terms they use. Don't confuse outcomes with predictions or determinants. The term patient-reported *outcomes* is used but people are often not thinking of outcomes when they write this, but are rather thinking of *predictions*. An outcome is something you expect to change or vary based on other factors. You should be clear

in what it is that you are reporting.

When writing, make sure that you distinguish between the proximal outcomes (i.e., symptoms and function) and the distal outcomes (e.g. quality of life). For example, with heart failure, shortness of breath and physical function are proximal outcomes, which are likely to change due to medical interventions. However, a distal outcome like quality of life might not be affected by the intervention, as aspects also relevant for this construct, like level of job satisfaction or environmental factors, are not targeted by the intervention.

A conceptual model well known within the German healthcare system is the one developed by Wilson and Cleary<sup>2</sup> a couple of decades ago. It is a basic model, but one which is very effective at classifying different measures

of health outcome. It might be useful for medical writers who are new to the subject of patient-reported outcomes to learn more about this model.

**MEW:** Any last comments?

**Prof. Rose:** I have always been a missionary for patient-reported outcomes. It is great that a journal like *Medical Writing* is concentrating on

the subject and helping to get the message about PROs out there.

## Conflicts of interest

The author is employed by Smith & Nephew.

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I have always been a missionary for patient-reported outcomes.



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# The UK pharmaceutical industry braces for Brexit, be it mild, severe, or doomsday

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## Abstract

Pharma-Brexit is on its way. The announcement of the European Medicine Agency's move to Amsterdam, various UK government white papers, and comments made by key stakeholders in the UK pharmaceutical industry have led to a wide range of predictions concerning Brexit. While many hope for a Norwegian-type situation where business as usual could continue uninterrupted, others fear that the uncertainty of a "no-deal" outcome has already started a domino effect that could lead to the UK pharmaceutical industry's collapse. This article argues that something inbetween is most likely and looks at what Brexit could mean in each scenario. It explores why and how both the EU and UK might work through a deal and how these challenges might still provide opportunities for medical writers.

## Introduction

Since the Brexit referendum on June 23, 2016, there has been a deluge of predictions on the possible ramifications Brexit might bring. Consequences of the impending UK break-up with the EU at midnight on March 29, 2019, range from the conservative to the hyperbolic. Based on currently available information, it is possible to deconstruct the effects of Brexit on the pharmaceutical industry to three scenarios:

- Mild, in which a deal is reached with little disruption to the present situation;
- Doomsday, where no deal is reached, likely leading to the rapid decline of the UK pharmaceutical industry; and
- Severe, which falls somewhere between the two.

As of 2014, the UK has been the sixth largest pharmaceutical producer in Europe.<sup>1</sup> Separation of UK industry away from Europe is likely to be harmful, due to the long-term limitations it would place on information flow, business and trade agreements, and workforce movement. If no deal can be reached, irrevocable damage would be caused by the separation, potentially propelling the UK pharmaceutical industry into a dark age. On the other hand, if a deal similar to the Norwegian model is accomplished, then the UK pharmaceutical industry could end up with a comparable situation to the present.

Even without these decisions being finalised, some effects of Brexit are already being felt. Prominent among these is a profound uncertainty regarding the free movement of people across the EU. Complicating the free movement of the workforce not only threatens a future shortage of workers in the UK pharmaceutical industry, but could also impede further foreign investment into the UK pharmaceutical industry.

Furthermore, while darkness shrouds the Brexit negotiations, uncertainty abounds. Organisations such as the European Federation of Pharmaceutical Industries and Agencies assert that limitations on the free movement of people would have a "negative impact on both the UK

and EU academic research and small and medium enterprises". Even the threat of limitations may already be having an effect on potential investors.<sup>2</sup>

The immediate effects of Brexit are impossible to predict and may only become visible once the long-term impacts of separation can be evaluated. The sooner more of the UK government's Brexit plan is revealed, the better the prospects for the pharmaceutical industry in finding stability.

## Mild Brexit

### Norway model

By far the most desirable outcome for the UK pharmaceutical industry would have been a deal comparable to the agreement reached between Norway and the EU, although it is possible that negotiations have already removed this option. The "Norway model" is arguably the least damaging option and provides the most stability for businesses.<sup>3</sup> It would allow the UK to remain a part of the European Free Trade Association (EFTA) and the European Economic Area (EEA) and therefore the UK would continue to have a similar level of free trade. The EFTA contains four states (Switzerland, Iceland, Norway, and Liechtenstein) and is part of the Schengen Area, but not party to the European Union Customs Union. There are indications that a post-Brexit UK could be accepted into this trading bloc. The EEA is the free-trade area between all the other EU member states. The Norway model of a Brexit deal would be attractive to "soft" Brexiteers, as it does not leave the UK having to renegotiate its trade deals and gives further freedom to make trade deals with other countries.

### The pharmaceutical industry and a mild Brexit

Although damage to business would be limited following a mild Brexit, some change would still be inevitable. The European Medicines Agency (EMA) is in the process of moving from London to Amsterdam to continue operations within the EU, as a direct consequence of impending Brexit.<sup>4</sup> This move away from London takes the competitive edge of proximity away from UK

pharmaceutical industry regulatory affairs officials and UK Medicines and Healthcare Products Regulatory Agency (MHRA) personnel. In addition, the European Commission has already outlined the requirement for a European-based Qualified Person and consideration of the UK as a “third country” in the running of clinical studies from the withdrawal date.<sup>5</sup> In a mild Brexit scenario, significant further divergence from the current status quo seems unlikely, other than the UK losing the role of rapporteur status in the market approval process for pharmaceuticals.<sup>6</sup> This would result in the MHRA no longer being involved in EMA decision-making, despite the obligation remaining to follow EMA rules.

While the current assumption by the EMA is that the UK will become a country outside of the EEA, significant disruption would not happen were the UK to adopt a Norway model.<sup>3</sup> Despite this, it is quite likely that in most mild Brexit scenarios the current regulatory frameworks will be largely maintained and there will be little impact on the UK pharmaceutical industry, aside from losing a certain amount of influence within Europe.

## Doomsday

With the prospect of no deal being reached, newspapers from across the political spectrum, within the UK and abroad, have painted very dark possible scenarios. The possible damage has been compared to post-war shortages (e.g. food, medicine, and power shortages<sup>7-8</sup>) within a few days after a no-deal Brexit, due to the UK’s dependency on “just in time” supply chains. In this “doomsday” scenario, the knock-on effects on food, travel, IT networks, and availability of personnel could stretch pharmaceutical industry contingency plans to breaking point.

### Armageddon and the pharmaceutical industry

The Governor of the Bank of England, Mark Carney, described a no-deal Brexit outcome as being “highly undesirable”,<sup>9</sup> but this does not begin to illustrate the potential devastation. The UK pharmaceutical industry, from Research and Development to Sales departments, could easily plunge into complete chaos. No deal could mean a short-term cessation of the free movement of skilled workforce, despite current promises of prioritised entry. There could be an impact on the movement of goods as well. The loss of momentum to cutting-edge research and development

programmes could reduce the contribution of UK scientists to progress.

With regards to the free movement of people, issues could include difficulties arranging meetings due to delays with visas, disruption to working conditions due to missing personnel, and resultant interruptions to goods and service chains. Arguably, larger pharmaceutical enterprises will have the capacity to survive long enough for the worst to pass. Smaller enterprises, on the other hand, could face the brunt of the damage, unable to fully secure a large enough skilled UK-based workforce to be financially viable. If so, the UK may experience a mass migration of pharmaceutical industry personnel to EU member states, as the barriers such a Brexit would create could be insurmountable for smaller pharmaceutical enterprises.

Furthermore, as the UK Business, Energy, and Industrial Strategy Committee has suggested, the UK has historically “disproportionately benefited” from EU funding for pharmaceutical research.<sup>10</sup> This is funding that cannot be matched by the UK government, especially under the worst-case doomsday scenario in which the country will already be under tremendous financial strain.

### Regulatory systems in disarray

Although UK exports to EU countries were valued at £15 billion as of 2015,<sup>1</sup> EU countries are unlikely to suffer in the long-term due to reduced availability of UK goods if no deal is reached. While short-term damage may be inevitable, given the ramifications to the UK, EU member states would be well-positioned to slowly assume any gap in the market. Although the decline would not be instantaneous in the event of no deal, there could be severe complications to the regulatory process of product development and approval. A marked delay in the UK’s access to the EU market, which for an industry brimming with competition from an ever-globalised world, could irreversibly damage a stalled UK pharmaceutical industry.

In the absence of a deal, one of the greater challenges to the UK pharmaceutical industry will be working out how trade could actually continue with the EU. If no deal occurs, the UK Business, Energy and Industrial Strategy Committee states that the UK will no longer be part of any EU agreement on 0% tariffs, and would be reliant on the World Trade Organization’s (WTO) Pharmaceutical tariff elimina-



tion agreement.<sup>10</sup> This stipulates that all signatories of the agreement are prohibited from the placement of tariffs on pharmaceutical products. In theory this protects the UK pharmaceutical industry, but the list of protected products has not been updated since 2010 (despite the agreement stating it should be updated every three years). Consequently, there are over 1,000 products awaiting introduction to the list.<sup>10</sup> This would greatly disadvantage the UK pharmaceutical industry when competing with EU member states. Without a deal, rapid revisions of the WTO agreement would have to occur for the UK pharmaceutical industry to survive.

Having no deal would, in all likelihood, be disastrous for the UK’s pharmaceutical industry, but would probably only dent the EU pharmaceutical industry in the short term.

## Severe: The most likely scenario

Given the importance of the UK pharmaceutical industry to both the UK and EU, it is most likely that both sides will make every effort to achieve a mutually-beneficial deal. However, the UK Business, Energy and Industrial Strategy Committee advises that there would be “no benefits from regulatory divergence”<sup>10</sup> in the



The immediate effects of Brexit are impossible to predict and may only become visible once the long-term impacts of separation can be evaluated. The sooner more of the UK government’s Brexit plan is revealed, the better the prospects for the pharmaceutical industry in finding stability.

pharmaceutical industry. It is difficult to imagine a post-Brexit scenario that would entirely protect the status quo. The most probable outcome of negotiations would likely be a moderate solution: one in which there is limited regulatory divergence, but the potential loss of EU funding and reduction in industry productivity. This depends on the extent to which Britain maintains its position within the single market.

**Regulation: An association agreement**

According to a white paper produced by the government, the UK is likely to propose an “association agreement” with the EMA.<sup>11</sup> This would involve the UK paying a fee to the EMA to remain under its jurisdiction and thus retaining the ability to apply for EU funding, although the UK would be unable to influence the “direction of these programmes”.<sup>12</sup> Moreover, while the white paper provided some clarification on the UK’s stance towards the EMA, the policy relating to the Clinical Trial Directive (legislation that guarantees the quality and safety of medicinal products in the EU; soon to become the Clinical Trials Regulation) remains unclear.<sup>13</sup> A move to withdraw the UK from the Clinical Trial Directive, which has been perceived in the UK as

being overly bureaucratic, is seen as a real possibility. A report conducted by consultancy firm, PricewaterhouseCoopers, has suggested that this could result in companies choosing not to include the UK in clinical study design, or to include the UK only at a later stage of development.<sup>1</sup>

**Funding and investment**

Currently, the UK receives significantly more in funding for scientific research and development from the EU than it contributes, and whilst an association agreement with the EMA would protect the UK’s right to apply for such funding, it seems unlikely that a favourable funding surplus will remain intact after Brexit. Although the treasury has committed to underwrite funding for projects applied for before the UK leaves the EU, the status of such projects after the UK has left remains unclear.<sup>12</sup> Hence, whatever the outcome of negotiations, the loss of funding that could have otherwise supported new research seems to be inevitable.<sup>14</sup> Furthermore, the UK has also been the greatest recipient in the EU of foreign direct investment, much of which depends on the UK’s ability to access the EU market and to attract the best

people – both of which could be under threat if the UK does not come to some agreement on the single market.

**Free trade**

The government has stated that it is committed to the idea of “frictionless trade” between the UK and EU,<sup>11</sup> and it seems likely that the two parties will agree on a “common rulebook”. The EU has already rejected the UK government’s proposal to impose EU tariffs on goods coming into the UK that are destined for the EU. Furthermore, it seems likely that the UK will have to choose between one of the two following options: either lose any existing free-trade agreements negotiated by the EU, such as those with Israel and South Korea,<sup>1</sup> but gain the ability to negotiate new free-trade agreements; or retain all existing EU-negotiated, free-trade agreements, but be unable to formulate new deals aside from the EU. The cost of any disruption to existing supply chains could be severe and has already prompted large pharmaceutical firms, such as AstraZeneca, to begin stockpiling medicines.<sup>15</sup> Hence, some level of disturbance, especially in the immediate aftermath of the UK’s exit from the EU, seems inevitable.

### Free movement of people

As with the mild and doomsday options, the free movement of people remains a deep cause for concern. The UK government has said unequivocally that this will end and that it will “be for the UK Government and Parliament to determine the immigration rules that will apply to people coming to the UK from the EU”.<sup>11</sup> There has been very little indication as to what these rules may be. Uncertainty regarding the status of EU nationals working in the UK pharmaceutical industry has already prompted some professionals within the sector to leave.<sup>14</sup> The EMA’s relocation to Amsterdam is indicative of this concern. Moreover, if the UK is unable to host the best talent from across the EU, this makes the UK less attractive for foreign investment.

### Severe: How the pharmaceutical industry might fare

Possible effects on the pharmaceutical industry could include reduced investment and funding, and higher costs due to disruption of existing supply chains. In fact, this disruption has already begun; the EMA, having already changed their HQ from London to Amsterdam, have now ended the EU’s contract with the MHRA for medicines evaluation. The disruption and dissolution of the UK’s role in pharmaceutical supply chains will provide a significant challenge to the future of the industry. It is worth noting that some of the potentially negative consequences of a moderate Brexit solution may be mitigated in the long term by establishing new supply chains and possibly more favourable FTAs.

### And what about regulatory medical writing?

We are all hoping that the global nature of regulatory medical writing within a global pharmaceutical industry, coupled with the predominant requirement for delivery in English, will help UK regulatory medical writing weather the storm, if there even is one. But is that a responsible attitude? Awareness of the wider picture within the pharmaceutical industry will help medical writers prepare for cracks that may appear – cracks that medical writing may even be able to assist in patching.

A consideration of the different Brexit threats to the UK pharmaceutical industry and possible opportunities for UK-based medical writing is summarised in Figure 1. Awareness of new UK regulations and learning to include writing to

these regulations – in the same way that non-US/EU countries are catered to – will position medical writers favourably if Brexit resolves with mild severity. UK medical writers can also draw from their experience with shifting timelines, working within contingency plans, and their ability to familiarise and work closely with multidisciplinary teams, whatever the outcome of Brexit. On the other hand, stocking up on paracetamol and filling the cupboards with tins of beans might be wise, too.

### Disclaimers

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

### Conflicts of interest

There are no conflicts of interest.

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Figure 1. Threats from mild, severe, and doomsday Brexit to the UK pharmaceutical industry, and opportunities for UK-based medical writers.

Abbreviations: CSR, clinical study report; eCRF, electronic case report form; EMA, European Medicines Agency; IB, investigator's brochure; MW, medical writer

Outcome	Threats posed to UK pharmaceutical industry	Opportunities for UK-based MWs
Mild	<ul style="list-style-type: none"> <li>EMA moves away from London to Amsterdam</li> <li>Fewer study centres in the UK</li> </ul>	<ul style="list-style-type: none"> <li>No immediate impact on MWs</li> <li>MWs used to working within global teams and site location does not affect working practices</li> </ul>
	<ul style="list-style-type: none"> <li>UK-based companies cease to be the global or European headquarters of Research and Development within global pharmaceutical companies</li> <li>Regulatory roadmaps for strategy in the UK are not forthcoming in a timely fashion</li> </ul>	<ul style="list-style-type: none"> <li>MWs familiar with constant restructuring, adapt to global regulatory arrangement, adaptable to new project team structures</li> <li>MWs adaptable and proactive in keeping to ambitious timelines under pressure</li> </ul>
Severe	<ul style="list-style-type: none"> <li>Teams or clients unavailable due to relocation commitments and different time-zones adding to the challenge of arranging meeting times</li> <li>Pharmaceutical industry outsourcing more short-term and sporadic</li> </ul>	<ul style="list-style-type: none"> <li>MWs familiar with working remotely, brokering agreements between team members, facing unexpected project changes, and working hours that adapt to their clients</li> <li>Freelance MWs can maintain a variety of clients, ideally based in different continents which leads to a varied client-base and a chance to widen experience</li> </ul>
	<ul style="list-style-type: none"> <li>More UK regulatory documents required since the UK becomes a separate regulatory territory</li> <li>UK suffers from supply problems with knock-on effects on timelines</li> </ul>	<ul style="list-style-type: none"> <li>MWs familiar with preparation of non-EU/US documentation leading to increased volume of work for MWs and job security for UK MWs</li> <li>MWs used to adapting to timelines and maintain communication with the team</li> </ul>
	<ul style="list-style-type: none"> <li>IT and communications disruption</li> <li>Economic difficulties, e.g. falling pound in the UK, problems with supply chains in the UK pharmaceutical industry, emergency cuts to skilled workforce</li> </ul>	<ul style="list-style-type: none"> <li>MWs adaptable to all communication methods and contingencies, including paper methods, since some territories still operate this way</li> <li>MWs more marketable with cheaper contracts, both globally and for the local market</li> </ul>
Doomsday	<ul style="list-style-type: none"> <li>IBs and CSRs threatened with fines for delay in public disclosure due to skilled workforce cuts and communication disruption extending document preparation timelines</li> <li>Intermittent IT problems lead to problems at the clinic with eCRFs and a knock-on to data cleaning and statistical table compilation as well as other issues</li> </ul>	<ul style="list-style-type: none"> <li>MWs show ingenuity in flexible timeline management</li> <li>MWs adapt to using whatever data is available and fitting in with contingency measures</li> </ul>
	<ul style="list-style-type: none"> <li>UK pharmaceutical industry reduces to a local sales force and the need for UK production of global regulatory documents disappears</li> </ul>	<ul style="list-style-type: none"> <li>MWs have excellent transferrable skills and many already work from home for global pharmaceutical companies. In desperate circumstances, if the UK-based parts of global pharmaceutical industry completely fold, UK MWs can work remotely for European or US companies, move to a different industry, or move to another country</li> </ul>

# Awareness of medical writing as a profession and its career prospects:

## A survey conducted among medical writers working for a global pharmaceutical company operating in India

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### Abstract

As medical writing (MW) is a growing profession in India, we assessed the awareness among professional medical writers (PMWs) about their job and career prospects. We conducted an anonymous survey among PMWs ( $N=192$ ) working in a global pharmaceutical company (Novartis Healthcare, India). The survey assessed their awareness level, education/skillset utilisation, and career aspirations. Results showed that the respondents ( $N=154$ ) were highly qualified (97% had a master's/PhD/equivalent degree) and experienced in the MW field. Only 10% were fully aware of MW as a profession before entering the field, which increased to 57% after joining the profession. PMWs (93%) indicated that their education/skillset was utilised from a good to great extent; their skills were transferable and most had grown within or across functional/operational domains. Most respondents indicated a desire to continue in the profession for at least 5 years (40% for 5 to 10 years and 34% for more than 10 years). Almost an equal proportion preferred to grow as functional (38%) or operational (39%) experts. With ample growth avenues and skillset utilisation, MW may be a rewarding long-term profession.



### Introduction

In India, the medical writing (MW) profession has grown steadily since 2005<sup>1</sup> and has expanded its horizons because of the availability of a large pool of skilled professionals, English speakers, and an advantage in cost. The overall estimated costs in generating medical content in India is 40% to 60% of the costs in the USA and Europe.<sup>2</sup> As the majority of MW is done in English – the *lingua franca* of the medical sciences – many pharmaceutical companies have set up dedicated MW departments in India.<sup>3</sup> Although most professional medical writers (PMWs) work within pharmaceutical industries, contract research organisations (CROs) or knowledge process outsourcing companies (KPOs) or as freelancers, there are other settings where they are employed, such as medical media companies, medical journals, academic institutions, scientific

societies, healthcare websites, and governmental organisations.<sup>4,5</sup>

There are different MW business models operating in India generating ample growth opportunities for MW professionals. Pharmaceutical companies typically have in-house writing teams integrated with medical or regulatory affairs departments. The advantage is that the writers work very closely with the authors or scientific teams and are privy to the company's product strategy and communication plan. Thus, the writers are better placed to support the stakeholders in putting the scientific messages or data into the right context. On the other hand, CROs or medical communications agencies work under a service delivery model, where they cater MW services to different pharmaceutical/healthcare companies and are generally not an integral part of their clients'



organisations. Some pharmaceutical companies follow a hybrid model, i.e., sourcing MW services from an economical location to internal clients based in different geographical areas. This business model offers a dual advantage, being in-house, medical writers are closer to company strategy and provide services in a cost-effective manner to internal teams.

The key attributes of a PMW include an understanding of medical science, a flair for writing, command of language, ability to identify target audiences, attention to detail, good analytical skills, stakeholder management, managing tight deadlines, and teamwork. Graduates and postgraduates in life sciences who have the right skills and aptitude make a good fit as PMWs. MW skills are transferable, providing for the ability to transfer from one writing domain to another. Working in regulatory MW gives the medical writer an overview of the entire clinical development process, so it is an ideal starting point for other careers in the pharmaceutical industry, such as regulatory affairs, clinical research, document management, and even marketing. Those in medical communications may move into editorial roles at publishing companies, medico-marketing, or into the medical information profession.<sup>6</sup> The growth avenues for medical writers are vast within a pharmaceutical or healthcare communications company or a CRO.

India has the second largest English-speaking scientific force in the world after the USA. There are thousands of new graduates with master's and PhD degrees adding to that pool every year.<sup>7</sup> Although the MW profession has been in India for a long time, the awareness about this profession among prospective job applicants/medical writers seems to be limited; unlike Europe and the USA where MW is an established profession. Furthermore, no information is available about how well-informed PMWs are about their profession, career prospects, and growth avenues within the profession. Hence, it would be interesting to know if PMWs working in India find MW a fulfilling/rewarding career path. To address these questions, we conducted an online survey among the PMWs working in the medical communications and the medical information departments of a global pharmaceutical company in India.

## Methodology

### Survey questionnaire

The survey consisted of 10 questions in English (Appendix). The questionnaire included multiple choice questions (check one or check all), Likert scales (1–10 scale; with 1–3: no/very little; 4–7: somewhat/good extent; 8–10: fully/great extent), and free text options where applicable. The survey questions evaluated the participant's background and three key themes: (1) MW profession awareness, (2) education/ skill set utilisation, and (3) career aspirations of PMWs.

The awareness theme included questions on (1) PMWs' level of awareness about the MW profession pre- and post-placement, (2) the source of their awareness, and (3) entry into the MW profession "by chance" or "by choice". Education/skillset utilisation in the MW profession was gauged by the tenure and number of roles experienced by the PMW. To evaluate career aspirations, we included questions such as (a) how long the PMWs would like to continue in the MW profession (1–3 years, 5–10 years or >10 years) and (b) how they would like to grow in this profession, either in a functional (senior/expert writer, scientific editor scientific/medical lead, etc.) or an operational role (people manager, account manager, project manager, etc.).

### Survey participants and conduct

The survey was conducted using the online tool SurveyGizmo®. The survey link was distributed by email to PMWs working in the medical communications and medical information departments of Novartis Healthcare Pvt Ltd, Hyderabad, India. The message included a cover letter explaining the survey purpose and duration and the contact details of those responsible in case of any questions or concerns. Participants

were requested to complete the survey within 1 week (deadline November 24, 2017). There was no compulsion to complete the survey, the respondents were allowed to leave questions unanswered, and responses were anonymous.

### Analysis of data

Data were analysed descriptively. A *post-hoc* analysis by the respondents' years of experience in PMW was also performed.

## Results

### Background of respondents

The survey was sent to 192 PMWs, 174 (91%) of whom attempted the survey, completing it fully or partially. Only 154 (80%) of the respondents who completed the survey were analysed further. The highest qualification that most respondents had was a master's (50%), followed by a doctorate (47%) in life sciences/pharmaceutical sciences, whereas only a few had a bachelor's degree (3%) in medicine or dentistry. Most respondents (32%) had MW experience of more than 5 years, followed by 25% with 3–5 years, 27% with 1–3 years, and 16% with less than 1 year.

### Awareness of the MW profession

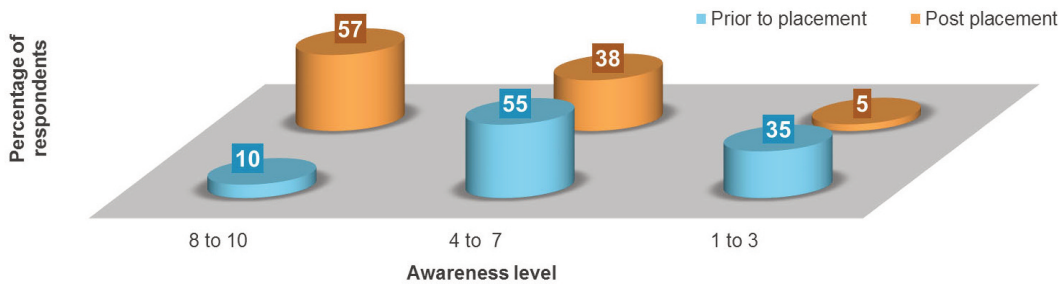
Respondents selected multiple channels through which they became aware of the MW profession. Among the predefined channels or free texts (others), the most common sources identified were seniors/friends/relatives (52%, n=80), followed by job portals/LinkedIn/newspapers (51%, n=78), and recruiters (22%, n=34) (Figure 1). A majority of the respondents (66%) entered the MW profession "by choice" and 34% "by chance".

The mean awareness level of the MW profession among the survey group during pre-placement was 5 (somewhat knowledge),



Figure 1. Sources of medical writing awareness

Question: how did you come to know about medical writing profession? Select all that are applicable.



**Figure 2. Respondents' awareness about the MW profession pre- and post-placement**

Scale, 1–10; 1–3: no or very little knowledge; 4–7: somewhat knowledge; 8–10: fully aware.

Question: prior to getting into the MW profession, how well you were aware of MW profession and its growth avenues, i.e., transferable skills across regulatory writing, scientific writing, medico-marketing, medical information, HEOR writing, grant writing, patent writing, etc.?

Question: currently, how well you are aware of MW profession and its growth avenues, i.e., transferable skills across regulatory writing, scientific writing, medico-marketing, medical information, HEOR writing, grant writing, patent writing, etc.?

Abbreviations: HEOR, health economics and outcome research; MW, medical writing

which improved to 8 (fully aware) post-placement. The survey group became more aware (scored 8–10) post-placement (57%) compared with pre-placement (10%) (Figure 2).

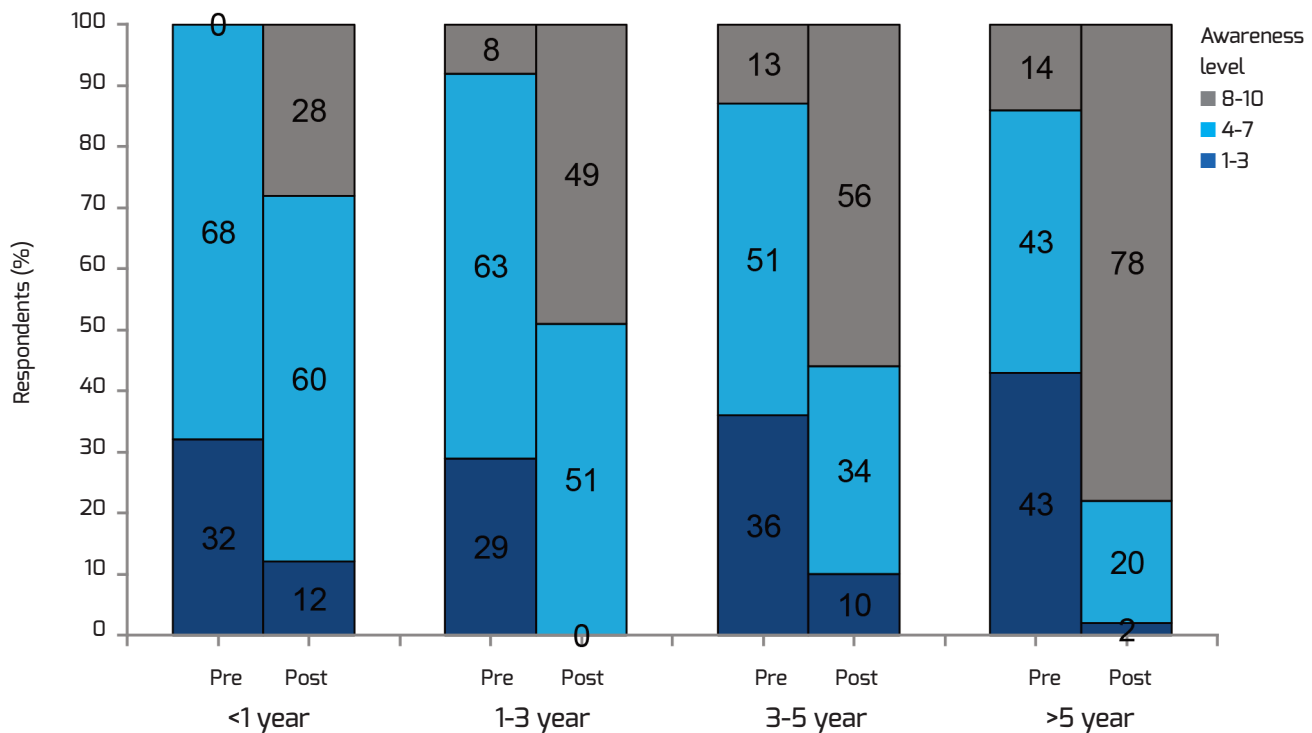
The subgroup analyses showed that with increasing years of experience, the awareness

(scale 8–10) of the MW profession increased; post-placement awareness percentage was high in the group with more than 5 years of experience (78% [38 of 49]), followed by 3 to 5 years (56% [22 of 39]) (Figure 3).

Apart from the core writing role, the different roles that PMWs most commonly switched to were people manager ( $n=31$ ) followed by project manager/specialist ( $n=25$ ) (Figure 4). The number of functional role switches ( $n=68$ ) was similar to operational role switches ( $n=75$ ).

**Education/skillset utilisation**

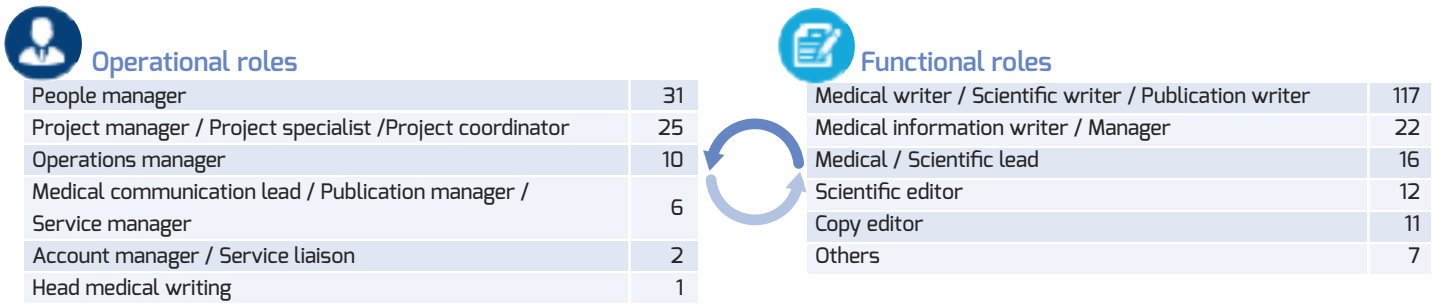
A total of 142 respondents (92%) had been in a core writing role (medical writer/scientific writer/medical information writer) at some point or another in their career. Whereas, 12 (8%) had a core project management background without any MW exposure. Sixty (39%) respondents had been in at least two different roles; of these, 46 (77%) had been in both functional and operational roles. The opportunity to switch to more than two roles was highest in MWs with more than 5 years (55%,  $n=33$ ) of experience, followed by groups with 3 to 5 years (25%,  $n=15$ ), 1 to 3 years (15%,  $n=9$ ), and less than 1 year (5%,  $n=2$ ) of experience.



**Figure 3. Awareness percentage across experienced groups pre- and post-placement in MW profession**

Scale, 1–10; 1–3: no or very little knowledge; 4–7: somewhat knowledge; 8–10: fully aware.

Abbreviations: MW, medical writing.



**Figure 4. Number of different roles PMWs switched during their MW career**

Question: which of the following roles in the medical writing profession you have been during your career path? Select all that are applicable.

Abbreviations: PMW, professional medical writer.

Most respondents (93%) indicated that their education/skillset was well utilised in the MW profession; 51% scored 8 to 10 (fully/great extent) and 42% scored 4 to 7 (somewhat/good extent) (Figure 5). The overall mean score for education/skillset utilisation was 7; among the different years of experiences, those with more than 5 years of experience scored 8, with 3-5 years of experience scored 7, and those with less than 1 year of experience scored 7. (Figure 5).

**Career aspirations**

Almost an equal proportion of respondents indicated that they would like to grow as a functional expert (38%) (senior/expert writer, scientific editor, scientific/medical lead, etc.) or as an operational expert (39%) (people manager, account manager, project manager, etc.). Some wanted to move outside the MW profession (13%), while a few (10%) did not have clarity about their future career paths.

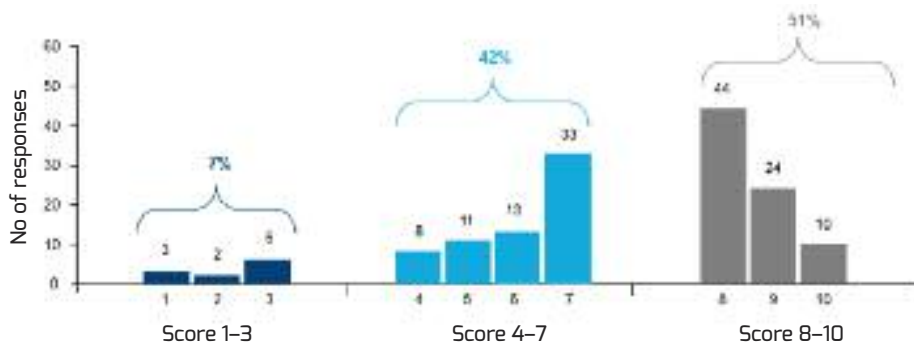
Overall, 61 (40%) of the respondents indicated that they would like to continue in the MW profession for 5 to 10 years, followed by 52 (34%) for more than 10 years (Figure 6).

**Discussion**

This survey was conducted amongst MW professionals who work for a global pharmaceutical company and represents one of the largest pools of medical writers in India. The survey results provide valuable insights on PMWs’ educational qualifications and experience, awareness level about the MW profession and its areas of growth, their education/skill set utilisation, and career aspirations. One limitation of this study is that the survey was restricted to Novartis associates only, which may limit the generalisability of the results.

The survey respondents were highly qualified and experienced MW professionals. There was a good mix of experience across junior to senior levels with most of them having more than 5 years or 3 to 5 years of experience in the MW profession. They also displayed an impressive range of degrees similar to another international survey group that included MW professionals from the USA and Europe.<sup>8</sup>

As evident from this survey, informal channels like seniors/ friends/relatives or job portals are the most common sources of information about the MW profession in India. Most respondents (90%) lacked full awareness about the MW profession prior to getting into the profession (pre-placement). However, post-placement, the mean awareness score increased from 5 to 8, i.e., the PMWs became fully aware about the profession. With experience, the level of awareness also increased. Although there was a lack of awareness pre-placement, about two-thirds of the respondents said that they entered this profession “by choice” and a few stumbled

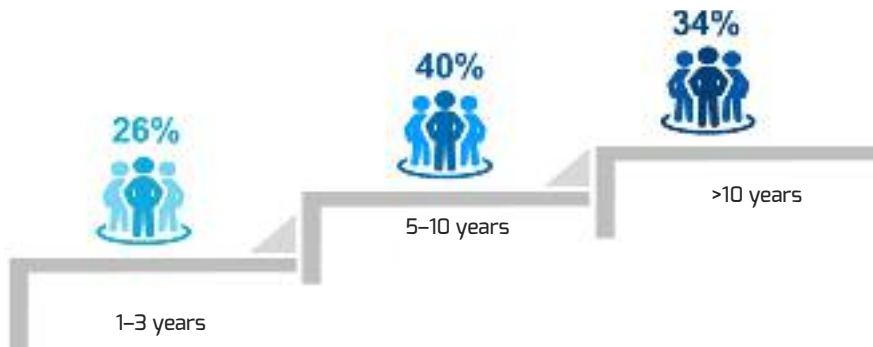


**Figure 5. Education/skillset utilisation among PMW**

Scale, 1–10: 1–3: no, very little; 4–7: somewhat, to a good extent; 8–10: fully, to a great extent.

Question: do you think that the MW profession provides you a platform to utilise your education and skills?

Abbreviations: MW, medical writing; PMW, professional medical writer.



**Figure 6. Percentage of respondents wishing to continue in the MW profession**

Question: how long would you like to continue in the MW profession?

upon this profession “by chance”. Notably, in another survey, the PMWs from the USA and Europe were well aware of the MW profession and had a clear rationale for choosing MW as their career. Most of them originally considered MW as a career because they “enjoyed writing” (70%), some thought that it fit their degree/previous experience (52%), some “wanted a change” (45%), a few (20%) said “flexibility” and “work-life balance”, and 25% had a “desire to help patients and advance healthcare”.<sup>8</sup> The lack of awareness in India could be due to the lack of formal education options in MW in academia or professional certification programmes.<sup>4</sup> This may restrict it to being a preferred career choice by life science or medical graduates compared with other professions.

In recent years in India, a few online MW courses have become available, and awareness about the MW field is being spread by MW associations through seminars and conferences.<sup>9, 10</sup> However, there is still a pressing need to create awareness about the profession and associated career prospects. As noted by Sharma, the awareness level may potentially be improved by (a) setting up certified, industry-led training programmes with a controlled curriculum, (b) providing internships to potential writing aspirants in reputable companies, (c) introducing scientific writing in the academic environment, (d) organising local MW conferences/ workshops/publications to increase awareness about the profession.<sup>1</sup> This may help to bridge the demand-supply gap and give career opportunities to an existing qualified and talented pool in India.

Most respondents (93%) said that their education/skillset was well utilised in their MW function regardless of whether they entered into MW “by choice” or “by chance” and found their career to be a fulfilling one. The education/skillset utilisation score was quite high across all experience groups, indicating that all the PMWs right from entry to a senior level were optimally engaged and had ample growth opportunities. There were many opportunities to switch into different roles both functionally and/or operationally; the number of roles that PMWs switched in their career was as high as six different roles. Apart from the growth within

their core writing role, 39% of PMWs had an opportunity to switch into at least two different roles; therein, 77% had been in both functional and operational roles. PMWs with more than 5 years in the MW profession had a higher number of role switches, maybe because of the long stint in the MW profession.

The highest number of moves made by PMWs were into people management or project management or medical/scientific lead roles. A few moves mentioned under the “others” category were medico-marketing, competitive intelligence, regulatory writing, and medical scientific liaison. This shows that the skills acquired in the MW role are transferable and one can move across the MW domain depending on one’s skill set and career aspirations. Like other developed countries, India has a good growth platform for medical writers. Regardless of the position one chooses as a starting point in a career within MW profession, there is a scope to change direction and to progress in different directions.<sup>6</sup>

A few years ago, many writers in India would join the profession but then move on to the “next big thing” after just a couple of years of writing, using MW as a gateway into the pharmaceutical company.<sup>10</sup> Our survey results show a shift in the trend, the majority of the respondents (74%) preferred to continue in the MW profession for more than 5 years and had equal preference to grow either as a functional expert (38%) or as an operational expert (39%). As evident from this survey, the skillset utilisation and the opportunities to grow as per PMWs’ aspirations may be the contributing factor for their choice to continue for long in this career. Moreover, compensation, job security, and working conditions are generally good with a good work-life balance in this profession.<sup>8,11</sup>

## Conclusions

In India, there is a rich pool of highly qualified and experienced PMWs. For many PMWs, the growth avenues and skillset utilisation may make MW a rewarding profession, motivating them to pursue it as a lifetime career. The results of this survey revealed that the awareness about MW among PMWs increased substantially post-

placement. However, there is a need to increase the awareness about the MW profession and its growth avenues among students/budding PMWs. This article gives direction to aspiring medical writers about the possible growth avenues, insights into the MW industry and the PMW talent pool available in India.

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No funding was received for this study.

## Conflict of interest

The authors are employees of Novartis.

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In India, the medical writing profession has grown steadily since 2005 and has expanded its horizons because of the availability of a large pool of skilled professionals.

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## Awareness About Medical Writing Profession

1. How long you have been associated with the Medical Writing field?

- < 1 year
- 1–3 years
- 3–5 years
- > 5 years

2. What is your highest educational qualification?

- Graduate degree (please specify, mandatory field)
- Postgraduate degree (please specify, mandatory field)
- Doctorate degree (please specify, mandatory field)

3. How did you get into the Medical Writing field?

- By chance
- By choice

4. How did you come to know about Medical Writing field? (select all that are applicable)

- Recruiters
- Seniors/friends/relatives
- College campus hiring
- Job portals/LinkedIn/newspapers, etc.
- Others (please specify)

5. Prior to getting into the Medical Writing field, how well you were aware of Medical Writing profession and its growth avenues, i.e., transferable skills across regulatory writing; scientific writing; medico marketing; medical information; HEOR writing; grant writing; patent writing, etc.?

- 1–3: no or very little knowledge
  - 4–7: somewhat knowledge
  - 8–10: fully aware
- |                       |                       |                       |                       |                       |                       |                       |                       |                       |                       |
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6. Currently, how well you are aware of Medical Writing profession and its growth avenues, i.e., transferable skills across regulatory writing; scientific writing; medico marketing; medical information; HEOR writing; grant writing; patent writing, etc.?

- 1–3: no or very little knowledge
  - 4–7: somewhat knowledge
  - 8–10: fully aware
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| 1                     | 2                     | 3                     | 4                     | 5                     | 6                     | 7                     | 8                     | 9                     | 10                    |
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7. Which of the following roles in the Medical Writing field you have been during your career path? (select all that are applicable)

- Medical Writer/Scientific Writer/Publication Writer
- Copyeditor
- Scientific Editor
- Medical Information Writer/Manager
- Medical/Scientific Lead
- Project Manager/Project Specialist/Project Coordinator
- People Manager
- Operations Manager
- Account Manager/Service Liaison
- Medical Communication Lead/Publication Manager/Service Manager
- Any Other (please specify)

8. Do you think that the Medical Writing field provides you a platform to utilize your education and skills?

- 1–3: no, very little
  - 4–7: somewhat, to a good extent
  - 8–10: fully, to a great extent
- |                       |                       |                       |                       |                       |                       |                       |                       |                       |                       |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| 1                     | 2                     | 3                     | 4                     | 5                     | 6                     | 7                     | 8                     | 9                     | 10                    |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

9. How would you like to grow in the Medical Writing field?

- As a functional expert (Senior/Expert Writer, Scientific Editor, Scientific/Medical Lead, etc.)
- As an operational expert (People Manager/Account Manager/Project Manager, etc.)
- Move outside Medical Writing profession
- Cannot say

10. How long would you like to continue in the Medical Writing field?

- 1–3 years
- 5–10 years
- > 10 years

### Appendix: Survey questions

# Estimands – closing the gap between study design and analysis

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## Abstract

Estimands represent a new way to look at key aspects of clinical research and will become increasingly important for medical writers. Estimands are detailed definitions of quantities to be estimated using clinical trial data, which make allowance for events that happen after randomisation. Such post-randomisation events include, for example, treatment discontinuation due to poor tolerability or lack of efficacy, and use of rescue medication. Through a worked example, this article elucidates several different kinds of estimands and shows how the estimands approach has the potential to improve the quality of clinical research. Estimands foster a more complete alignment of study objectives, study design, study conduct, data analysis, and interpretation of results.

The word *estimand* may look like a spelling mistake, but it actually represents a new paradigm in clinical research. With the new term comes a set of concepts that will change the way we perform clinical studies, particularly pivotal phase III studies. Estimands are not really a statistical idea, but rather one that pertains more generally to the evaluation of clinical trial results.

Clearly the word estimand is related to “estimate”: an estimand is a clinical entity or parameter that is estimated by performing a

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This is an updated version of an article that appeared in the *AMWA Journal* 2017;32(4): 156–60.



clinical study. In other words, an estimand is the *target* of estimation; the aim is to capture this target of estimation as precisely as possible. The concept of estimands is the subject of lively discussion in the statistical community and is outlined in a recent draft addendum to the International Council for Harmonisation (ICH) guideline on statistical principles for clinical trials, ICH E9.<sup>1</sup> In the months after its release for public consultation at the end of August 2017, a number of organisations and individuals submitted comments and suggestions on the draft addendum to the EMA.<sup>2</sup> The ICH E9(R1) Expert Working Group recently released a collection of training materials that elaborate on the content of the addendum and make suggestions on its implementation.<sup>3</sup> The final version of the addendum is expected in 2019.

## Randomisation and intercurrent events

Given the effort and cost involved in conducting a clinical study, we want to be sure it produces objective results that have not come about by any systematic error that shifts the results in a certain direction. A central method to avoid bias is randomisation. By randomly assigning the patients in a study to two parallel treatment groups, we ensure that the two groups are comparable at study start with respect to both known (measured) and unknown characteristics.

Then we can safely ascribe any effect we see to the treatment we are investigating – or at least, that is the common belief. In fact, however, this is only true if the initial randomisation is maintained during the study – and that is often not the case because of “intercurrent events”,<sup>4</sup> for which a better term would be “post-randomisation events” (the two terms are used interchangeably in this article).<sup>2</sup> These are any events that happen to patients during a study and that may affect the results. In particular, the following intercurrent events are important: patients die, they stop taking the study medication because they experience side effects or because they feel they are having no benefit from the treatment, or they take additional medication that will interfere with the efficacy endpoints (Figure 1).

Randomisation ensures that the variation among individuals is similar in the two treatment groups at baseline. However, each individual patient is likely to experience different intercurrent events depending on which treatment he or she receives. This may result in differences in the rates and timing of intercurrent events between the treatment groups. If we exclude all patients who experience intercurrent events from the analysis then we may, at the time when the study results are determined, no longer have treatment groups that are comparable. This is why, until now, industry guidance (ICH E9) has recommended performing an intention-to-treat

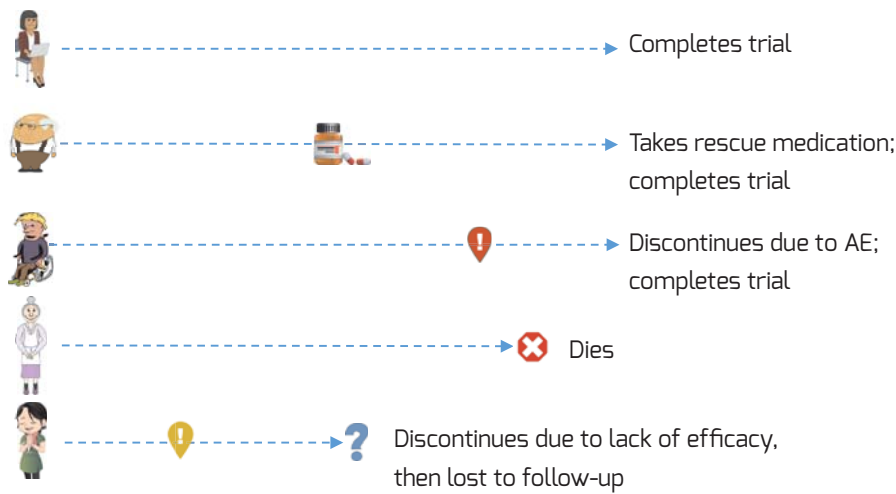


Figure 1. Examples of post-randomisation events that may occur in a group of patients

(ITT) analysis on all randomised patients, or at least, as close to all randomised patients as possible. The new addendum to ICH E9 recognises that this guiding principle has its limitations.<sup>4</sup>

### Effects of post-randomisation events

The potential effect of post-randomisation events is best illustrated with an example. Assume we have a study in patients with type 2 diabetes and we want to compare two treatment groups: one group receives wonderdrug (WD) and the other group receives placebo, both in addition to background therapy. We want to measure the treatment effect by comparing the reduction in glycated haemoglobin (HbA1c), a long-term marker of blood glucose levels, from study start to Week 26.

In trials in type 2 diabetes it is standard to make rescue medication available to patients whose blood glucose level is not adequately controlled with the study treatment. This means that patients whose blood glucose exceeds a predefined limit are allowed to take additional antidiabetic medications alongside the study treatment. This is done because high blood glucose increases the risk of complications such as cardiovascular problems or damage to the nerves, kidneys, or eyes. It would not be ethical to require patients to continue in the trial with excessive blood glucose levels.

However, from a scientific point of view, the use of rescue medication in a trial complicates the evaluation of the treatment effect. The question

is what to do with the data when patients start taking rescue medication. Do we continue to take efficacy measurements in these patients, and do we include such measurements when we calculate the treatment effect?

Clearly our decision with regard to trial design will have consequences for how we need to interpret the results. Up to now, such consequences have not always been considered at the trial design stage.<sup>5</sup> For example, if we plan the trial in such a way that data are not collected from patients after they have started rescue medication (e.g. because such patients are withdrawn from the trial), then we may end up with only a small number of patients with data at Week 26. Our options at the analysis stage will then be limited; a full ITT analysis will not be possible. If, on the other hand, we collect and use data from all patients, even after rescue medication use (i.e., the ITT approach), then the measured values will reflect both the effect of the study treatment and the effect of the rescue medication, resulting in a comparison of WD plus rescue medication and placebo plus rescue medication. Depending on which option for the collection and analysis of data is chosen, the precise definition of the treatment effect (or estimand) will differ. Although using the ITT approach helps to ensure statistical validity, the estimate of treatment effect it produces may not be clinically meaningful because the effect of WD will be “blurred” by the effect of rescue medication. This situation has been described in terms of a trade-off between “having a precise answer to a less relevant question or an approximate answer to the most

relevant question.”<sup>6</sup> The estimands discussion makes clear that this trade-off can be made in a variety of different ways.<sup>3</sup>

### The new approach: Estimands

Rather than arriving at a particular estimand implicitly and haphazardly as a consequence of choices about data collection and statistical analyses, the ICH E9 addendum suggests that we should consider explicitly and up front the various scientific questions that the trial data could be used to address. Using estimands allows us to see intercurrent events as a source of important additional information on the efficacy and safety of an investigational treatment, rather than treating them as a nuisance or complication.<sup>7</sup>

We can then choose which questions – and hence estimands – are the most meaningful in our clinical context and which are most relevant for patients, their doctors, regulators, and payers. The disease setting and aim of treatment will affect the choice of estimands.<sup>3</sup> In many settings, a single estimand is unlikely to meet the different needs of all stakeholders.<sup>8, 9</sup> It has even been proposed that the most helpful way to provide physicians and patients with the information they need about a treatment would be to include a (lay) description of several estimands in the prescribing information.<sup>5, 6</sup>

Compared with endpoints as currently defined in clinical trial protocols, estimands are more detailed definitions of the quantity to be estimated and comprise four interrelated attributes, described in the ICH E9 draft addendum as follows:

- **Population:** Which patients are targeted by the scientific question?
- **Variable/endpoint:** Which quantity needs to be obtained for each patient to address the scientific question?
- **Intercurrent/post-randomisation events:** How are these to be accounted for to reflect the scientific question?
- **Population-level summary:** Which summary statistic (e.g. mean or median) for the variable will be the basis for comparing the treatments?

In our diabetes example many different estimands are possible, and the situation would become even more complicated if we were to consider other kinds of intercurrent events (e.g., deaths and discontinuations due to adverse events) in addition to rescue medication use.<sup>3, 10</sup> Estimands could also be defined for answering questions

**Table 1. Three possible estimands for a trial in type II diabetes**

	Endpoint Variable	Intercurrent/Post-randomisation Event
Estimand 1 (treatment policy)	Change in HbA1c from baseline to Week 26	Consider all data regardless of rescue medication use
Estimand 2 (on-treatment)	Change in HbA1c from baseline to Week 26 or to the last value before initiation of rescue medication	Data after initiation of rescue are not considered
Estimand 3 (hypothetical)	Change in HbA1c from baseline to Week 26	Data after initiation of rescue are modelled as if no patients took rescue medication before Week 26

The estimand descriptors given in brackets are the terms used in the draft ICH E9 addendum.

related to safety, e.g. How long are patients able to remain on the treatment before discontinuing due to adverse events?

To keep things simple, we will look at just three types of estimands for the treatment effect that deal with rescue medication use in different ways (Table 1). (The draft version of the ICH E9 addendum actually defines five different types of estimands.)<sup>1</sup> All three estimands define the same patient population (i.e., the one in which it is planned to use WD after approval, as reflected by the trial inclusion and exclusion criteria), and all use the difference in mean change in HbA1c values between the treatment groups as the “population-level summary”. The differences among the estimands lie in the precise definition of the variable to be used as the primary endpoint and in the handling of the intercurrent event “use of rescue medication”.

**Estimand 1** is the estimand corresponding to the ITT analysis described in the previous section, and requires that we use the HbA1c data from all patients at Week 26, including those who have started rescue medication (Figure 2). If WD is effective at lowering HbA1c, then we can expect that the use of rescue medication will be more frequent in the placebo group. The treatment effect we estimate at Week 26 will then be the difference between the effect achieved by WD, occasionally with additional rescue medication, and the average effect seen in a placebo group where many patients are taking rescue medication known to be effective in reducing HbA1c.

Given the blurring of the efficacy of WD by the use of rescue medication in the control arm, we may end up with a modest difference between

the treatment groups that underestimates the true difference between WD and placebo. On the other hand, we will obtain a result that reflects clinical practice “out there”, because it is very likely that some patients in clinical practice will require additional medication, whether they are taking WD or other standard antidiabetic medications. Such an approach is called a “treatment policy estimand”, and this analysis is likely to be of particular importance to payers and reimbursement agencies who want to know the effectiveness of WD in the real world. This is also sometimes called an “effectiveness estimand”.<sup>11</sup>

Analysing all patients according to the treatment they were randomised to, rather than

the treatment they actually received, helps to ensure that the treatment effect is not overestimated and that statistical tests produce valid results. In 2011, a US FDA reviewer used precisely this argument to suggest that the most valid way to analyse data for the new antidiabetic drug dapagliflozin was to use all data, including values from patients taking rescue medication, in the statistical model.<sup>12</sup> This incident was a trigger for the estimands debate.<sup>4,10</sup>

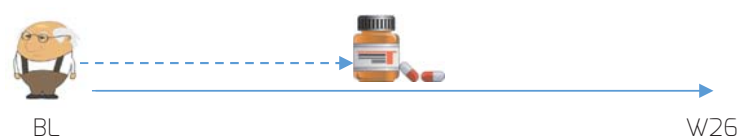
**Estimands 2 and 3** attempt in different ways to capture the effect of WD itself without blurring it by the use of rescue medication.

**Estimand 2** considers all data up to Week 26 or the time when rescue medication was initiated (Figure 2). It estimates the effect of the treatments until rescue was needed or until Week 26 for patients who did not need rescue medication. If WD works, few patients in this group will need rescue medication, and those who do need it are likely to need it late in the trial. Conversely, in the placebo group many patients will need rescue because their background medication will not control blood sugar effectively and they are likely to need to initiate rescue medication soon after study start. Using the last recorded HbA1c value before start of rescue medication means this analysis will use values for many patients, particularly in the placebo group, at a time point when HbA1c values are likely to be high. This estimand will therefore have a tendency to overestimate the

Estimand 1 = change from BL to W26 regardless of rescue medication use:



Estimand 2 = change from BL to last value before rescue medication:



Estimand 3 = change from BL to W26 as if no patients took rescue medication:



**Figure 2. How three estimands account for rescue medication use.** BL: baseline; W26: Week 26



## How will estimands affect medical writers' work?

- Medical writers may come across estimands while writing study protocols. Estimands will need to be described for the primary and key secondary endpoints. Study objectives, study endpoints, and the analysis methods for the results will need to be closely aligned and described in detail. To this end, estimands will need to be agreed upon cross-functionally at the early stages of protocol development. Medical writers will need to understand estimands to facilitate this process.
- In the study protocol and the case report form, the reasons for discontinuation of

treatment will need to be captured with greater granularity. In the informed consent form, patients will need to be asked for consent for data collection to continue if they decide to discontinue treatment.

- In clinical study reports, the methods sections for the description of study design and objectives, choice of endpoints, and analysis strategy will need to outline the estimands chosen. The results sections will need to be organised around estimands in addition to endpoints, and will need to describe the occurrence and timing of post-randomisation

events. Reports will also need to include discussion of any limitations of the chosen estimands and of how unforeseen post-randomisation events were handled in the analysis.

- Writers of clinical submission documents will need to describe estimands comprehensively to justify the choice of patient population and endpoints for the proposed drug label.

Guidance on the documentation of estimands is included in the ICH E9 addendum training materials.<sup>3</sup>

effect of WD.<sup>10</sup> Such an approach is categorised as an “on-treatment” estimand because it estimates the response to treatment prior to the occurrence of the intercurrent event.<sup>1</sup>

In effect, Estimand 2 corresponds to a last-observation-carried-forward (LOCF) analysis. Although LOCF has been widely used to deal with rescue medication in type 2 diabetes trials, it is a problematic approach because it results in estimates that are biased.<sup>13</sup> Bias may also be a disadvantage of Estimand 2, and the resulting estimate will be difficult to interpret because it is based on a comparison of data at widely different time points in the two treatment groups. However, in some clinical trial settings, such as the evaluation of palliative treatments in end-of-life care, where death is an expected post-randomisation event, a while-on-treatment estimand may be the most clinically meaningful one.<sup>3</sup>

**Estimand 3** provides a very different and less intuitive, yet interesting approach. With this estimand we estimate the treatment effect that would be seen if no patients took rescue medication (Figure 2). The analysis for Estimand 3 will include only values from patients who have not (yet) started rescue medication; HbA1c values will be counted as missing from the point when a patient starts rescue medication. An appropriate method for handling missing data through statistical modelling (e.g. multiple imputation [MI] or mixed models for repeated measures [MMRM]) will need to be used.<sup>10,13</sup> The resulting estimate will reflect both what actually happened in patients who reached Week 26 without rescue medication and what the data collected before rescue medication suggest might

have happened by Week 26 in the remaining patients if they had continued without rescue medication. This estimand is hypothetical at the level of a group of patients: it relies heavily on the modelling of the data for a large proportion of patients and will therefore never fully reflect a “real-life” situation. The usefulness of this type of estimand has been contested, particularly by health technology assessment agencies responsible for assessing the value of a treatment in actual clinical practice.<sup>2</sup> The ICH E9(R1) Expert Working Group advises that hypothetical estimands should be based on clinically reasonable situations that are clearly specified in the clinical study protocol.<sup>3</sup> Based on appropriate statistical modelling, Estimand 3 is likely to provide a less biased answer than Estimand 2 to the question that is crucial to individual patients: “If I take this drug as part of my treatment regimen, without adding any further drugs, what effect can I expect to see after 26 weeks?”

### Estimands and trial design

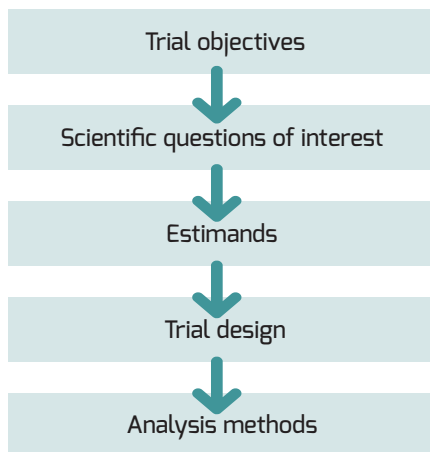
We have tried to make it clear that estimands will help researchers to formulate more clearly what they really want to get out of a clinical study. The traditional approach does not adequately take into account the effects of intercurrent events on the primary endpoint measure.<sup>4</sup> As demonstrated in the example of rescue medication use in a type 2 diabetes trial, depending on how we account for such events, we may be aiming to estimate the effect of the study drug itself or we may actually be evaluating a treatment policy.

In the past it was often the case that clinical researchers tried to elucidate what exactly they

had evaluated after a study had been completed. This is surely not the ideal situation because very little can be done after the fact. For example, once the decision has been taken not to collect data after initiation of rescue medication, this cannot be reversed after trial completion.

The paradigm shift introduced by the idea of estimands involves a different sequence of activities (Figure 3).<sup>3,5,9</sup> Clinical researchers first need to think about the objectives of the trial (i.e., what the trial is meant to show). An objective could be to demonstrate the effectiveness of a drug in reducing HbA1c in patients with type 2 diabetes. Researchers then need to consider the precise scientific questions of interest to be addressed and to choose estimands that answer these questions. In order to ensure that key stakeholders' needs are met, this choice should be made in discussion with regulatory authorities and in accordance with available guidance.<sup>2,3</sup> Indication-specific guidelines on the appropriate use of estimands are likely to become available in the future. Once the estimands have been defined, the trial can be designed in such a way that all the necessary data are collected, and the statistical analysis methods can be chosen to address the estimands of interest. For many estimands relevant to patients and physicians, it will be necessary to record reasons for treatment discontinuation more rigorously than has tended to be done up to now. For example, collecting reasons for study discontinuation such as “lost to follow-up” or “investigator decision” will become completely inadequate. These broad categories do not permit the calculation of important estimands.

Questions about the probability of a patient discontinuing treatment due to tolerability issues on the one hand or due to lack of efficacy on the other can only be answered if detailed reasons for discontinuation are captured.<sup>6</sup>



**Figure 3. The proposed role of estimands in clinical trial design**

Choosing the appropriate estimand for a given trial objective is primarily a medical and clinical question and not a statistical one. Indeed, some prominent statisticians go so far as to proclaim that estimands are not a statistical topic!<sup>4</sup> In any case, discussion between medical and statistical experts will be necessary to ensure that the estimands chosen reflect questions of clinical interest and can also be estimated statistically.

In good clinical research it was always the case that researchers started the planning of a trial by defining its objectives. They also chose endpoints and a statistical methodology. However, the potential influence of intercurrent events on the interpretation of the endpoints was rarely considered. Estimands close the gap between the trial objectives and the main estimates by clarifying exactly how intercurrent events will be considered or how the interpretation changes when those events are considered in different ways.

## Disclaimers

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

## Conflicts of interest

The authors declare no conflicts of interest.

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# Protecting the rights of clinical trial patients through disclosure: The significance of plain language

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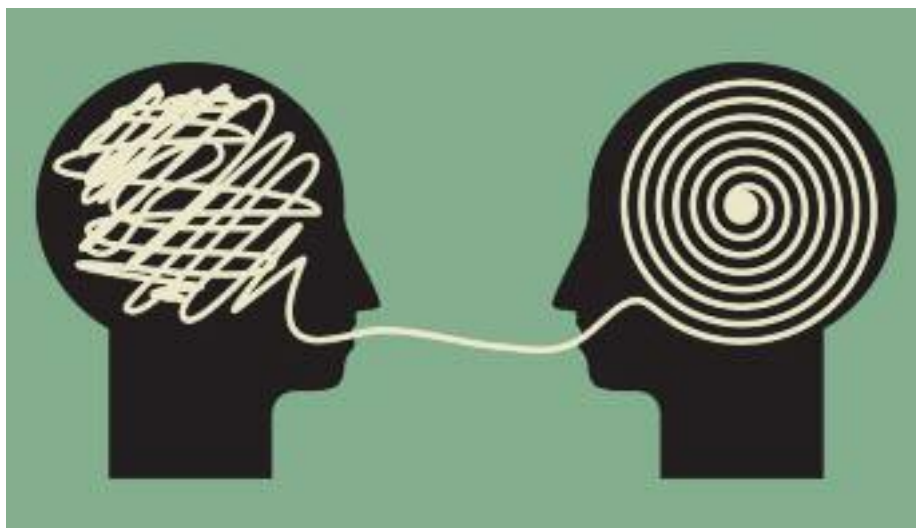
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## Abstract

Taking a step back to understand the history of clinical trial regulation triggers a broader perspective on the work we do or the work we will do. As regulatory medical writers, our role is often limited to the more technical submission-level component of either a trial design or a trial outcome. With the advent of plain language summaries (also known as patient lay summaries), we have a unique opportunity to inform the clinical trial patient population directly, and in turn the wider public audience.

Medical writers come from diverse backgrounds with varying professional roles, frequently serving as subject matter experts in a particular niche of the field. Writing skills and technical understanding are developed and broadened over many years. Looking back on the early days of my own medical writing career, some scientific aspects of medical writing were intimidating. Whilst working for an early phase unit, I attended presentations on introductory statistics and pharmacokinetics that were given to a cross-functional group in lay terms (i.e., *plain language*). This plain language explanation of complex topics made a lasting impression and the newly acquired knowledge instilled confidence during my early career. Consider that the use of plain language is vital when communicating with an audience of unknown and varied backgrounds



because it facilitates understanding and aids retention.

Clinical trial volunteers certainly qualify as an audience of unknown and varied backgrounds whose need for clarity may be heightened by their clinical condition. In the US, readability studies suggest that consumer comprehension is compromised when content exceeds a seventh-grade reading level, which is the average American reading level as identified by the United States Department of Health and Human Services.<sup>1</sup> As potential authors of clinical trial plain language summaries, it is important to achieve an understanding of health literacy and its impact on readability by region as this is a known variable across the trial volunteer audience.

In the June 2018 issue of *Medical Writing*, we read invaluable information about the writing process for clinical trial disclosure documents, including the bookmark-worthy “Writing lay summaries: What medical writers need to know”.<sup>2</sup> Here, the intent is to further explore the topic of plain language in the context of clinical trial patients’ rights, sponsor responsibilities, and the medical writer’s role in delivering transparency.

## Where it all began

The FDA was founded as a scientific institution

in 1848, and the US Congress passed the Pure Food and Drugs Act in 1906. Thereafter, legislation gradually required greater accountability for marketing food and drugs; this in turn increased the need for testing drugs in clinical trials.<sup>3</sup> The EMA was founded in 1995 as a partner of the European Commission and regulatory authorities within individual countries. Both the FDA and the EMA, often in partnership with patient advocacy organisations, have been influential in advancing the concept of clinical trial disclosure.

The history of clinical trial participation and patient protection is a fascinating and a troubling one, often triggered by significant national and global tragedies, or human abuses.<sup>4,5</sup> By the early twentieth century, clinical trials had come under increasing government regulation as authorities recognised a need to better control emerging medical therapies.<sup>3</sup> To date, several milestones have led us to where we are today, beginning with the Universal Declaration of Human Rights after World War II through to the 1996 International Conference on Harmonisation (ICH) Good Clinical Practice guidelines (Table 1).

Health literacy has been defined as “the degree to which an individual has the capacity to obtain, communicate, process, and understand basic health information and services to make

appropriate health decisions.”<sup>7</sup> Globally, when health literacy is low, a patient’s ability to make appropriate informed health decisions is diminished. The use of clear terms and language that the lay person can fully understand is vital with nearly half of US adults having difficulty accessing, understanding and utilising health information.<sup>7</sup>

The use of plain language has been advocated across several decades and disciplines. Toward the end of the twentieth century and start of the twenty-first century, tangible outcomes of this advocacy started to emerge. In 1977, the *New York Times* published an article, “The Plain Language Movement is Gaining”, which reported that attempts to simplify legal language dated as far back as the third US president, Thomas Jefferson.<sup>8</sup> At that time and with the growth of consumerism, an accelerated movement for plain language had gained momentum resulting, for example, in a New York state law that required clear and understandable language in contracts such as apartment leases and loan agreements. However, the article also warned that the path to simplification is hazardous as the standard of simplicity had not been defined. At the time, critics of plain language believed that complex ideas could not always be expressed in language that is simple.<sup>8</sup> Although critics of plain language exist today, they are more outnumbered than ever before.

This brings us to the next series of important milestones in the timeline of the ethical protection of patient rights – international regulations for clinical trial registration<sup>9</sup> – which in turn led to clinical data transparency or, more specifically, plain language summaries, also known as patient lay summaries. These regulations will enable clinical trial participants to understand what *will* happen and what *did* happen during a clinical trial in which they participated.

In 1998, Dave Skinner of the Translation Service European Commission published a poem titled *Clarity*. In the poem, he muses that we frequently talk about transparency, yet we proliferate opacity, when what we need is clarity – which he further specifies as “abandoning obscurity / And preferring more simplicity”. He advises: “Write English as it ought to be”.<sup>10</sup>

### Current patient expectations

The Center for Information and Study on Clinical Research Participation (CISCRP) is a non-profit organisation in the US, committed to educating patients and the general public about the importance of the clinical research process.<sup>11</sup> In a 2017 study on public and patient perceptions, CISCRP found that many patients (74% of 12,427 respondents) were interested in discussing clinical trial participation within an online-peer community. This tells us the signi-

ficance of patient expectations regarding information accessibility. While 84% of respondents indicated that it was important to be aware of clinical trials being conducted in their community, approximately 40% were not confident that they could find an appropriate clinical study. Survey participants were also asked the following question: “How much do you trust pharmaceutical companies to give full and accurate information about the health risks and benefits of new medicines?” Just over half (53%) responded “some” and approximately 25% responded “not too much”.<sup>11</sup>

The EU Clinical Trials Regulation 536/2014 states that trial sponsors should provide a clinical trial results summary in a format understandable by a lay audience. While the US encourages sponsors to provide plain language summaries, this requirement was not included in the Final Rule (FDAAA 801).<sup>9</sup> When the regulatory requirements and recommendations are combined with patient expectations relevant to clinical trials, the critical nature of public disclosure comes into distinct focus.

### Resources to improve transparency

In the field of medical and health research, English translators at the European Commission authored *Fight the Fog* in 1998, a publication that

Table 1. Important milestones in regulating the ethics of medical research

Year	Milestone
1947–1948	Nuremberg Code 10 principles on the ethical conduct of medical research involving human subjects; first international guidance which resulted from the mistreatment of prisoners in Nazi concentration camps during World War II. <sup>3</sup> Universal Declaration of Human Rights (adopted by the General Assembly of the United Nations) substantiated global concern regarding the involuntary maltreatment of human subjects.
1962	Kefauver-Harris amendments proposed greater federal oversight to ensure the FDA review claims of efficacy (versus safety alone) before drug approval, monitor pharmaceutical advertising, and ensure that all drugs had readable generic names. <sup>6</sup>
1964	Helsinki Declaration developed by the World Medical Association as a list of ethical principles that serve as guidance for clinicians and clinical trial human participants, material, or data.
1966	International Covenant on Civil and Political Rights, a human rights treaty adopted by the United Nations to protect the civil and political rights of individuals. “In particular, no one shall be subjected without his consent to medical or scientific treatment”.
1974	US National Research Act authorised federal agencies to develop regulations for human research.
1979	Belmont Report released by the US National Commission documented key principles of ethical research and influenced research ethics regulations in the US.
1991	The Common Rule (45 CFR 46) established regulatory framework applicable to all US federal agencies.
1996	International Conference on Harmonisation published Good Clinical Practice, which remains the industry standard for the ethical conduct of clinical trials.

Source: Bhatt A. Evolution of clinical research: a history before and beyond James Lind.<sup>3</sup>

consisted of simple suggestions to “put the reader first”.<sup>12</sup> In the US, the Centers for Disease Control (CDC) published the *Plain Language Thesaurus for Health Communications* in 2007<sup>13</sup> and later in 2016 *Everyday Words for Public Health Communication*.<sup>14</sup> The CDC publications provide lists of “frequently used terms in public health materials and their common, everyday alternatives in plain language sentences”. These are important and relevant tools designed to encourage the use of easy-to-understand language when communicating complicated health information to the general public.

A quick guide to health literacy, published by the US Department of Health and Human Services,<sup>15</sup> identified the key elements of plain language as:

- Organising information so that the most important points come first
- Breaking complex information into understandable sections
- Using simple language and defining technical terms
- Using the active voice.

The use of plain language is just one of many components to improve health literacy. Several resources are available to improve clinical data transparency via the plain language summary of trial results (Figure 1).

**Figure 1. A word cloud of clinical trial plain language summary resources**



## Time to get on board

As new scientific disciplines and technologies become part of drug development, the regulatory and ethical landscape will continue to evolve.<sup>3</sup> As a globally-connected society, well into the digital age, our expectations have shifted with the advent of accessible and contemporaneous information,

particularly in developed countries. Most in the medical writing community are accustomed to scientific writing within the confines of regulatory requirements, and we now have an exceptional opportunity to inform alternative audiences. Armed with the legacy of plain language, and keeping clarity in mind, we may influence perceptions of clinical research and make a difference in the lives of patients and those of the wider population.

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## Disclaimers

The views expressed in this article are those of the author and do not necessarily reflect those of EMWA.

## Conflicts of interest

None

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# News from the EMA

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

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## EMA identifies gaps in industry preparedness for Brexit



**July 10, 2018** – A recent European Medicines Agency (EMA) survey shows that marketing authorisation holders for more than half (58%) of the 694 centrally authorised products (CAP) with an important step in their regulatory processes in the United Kingdom (UK), are on track with their regulatory planning to ensure that their marketing authorisation remains valid once the UK leaves the European Union (EU).

Regulatory authorities and marketing authorisation holders both play an important part in preparing for the consequences of Brexit to safeguard the continuous supply of human and veterinary medicines after the withdrawal of the UK from EU. Since May 2017, the European Commission and EMA have informed companies and raised their awareness of the need to put the necessary measures in motion. Information notices on legal issues and guidance on practical and simplified requirements for companies have been published and regularly updated.

For marketing authorisation holders of CAPs, this may imply changes to the marketing

authorisation itself, including, for example, a transfer of the marketing authorisation to a legal entity established in the European Economic Area (EEA), or a change of the qualified person for pharmacovigilance (QPPV) or pharmacovigilance system master file (PSMF) to a location in the EEA, as well as adaptations to their logistics, manufacturing sites, supply chains and contracts.

However, for 108 (88 human products and 20 veterinary products), or 16%, of these medicines with manufacturing sites located in the UK only, there are serious concerns that the necessary actions will not be carried out in time.

For 10% of the products included in the survey, EMA received no feedback from companies.

The aim of the survey, which was launched in January 2018, was to identify CAPs that are potentially at risk of supply shortages and to obtain information on the timelines for submission of the necessary regulatory changes. The survey was sent to marketing authorisation

holders of the 694 CAPs (661 human and 33 veterinary products) who are located in the UK or who have quality control, batch release and/or import or manufacturing sites, or a QPPV or PSMF in the UK.

According to EU law, the marketing authorisation holder, the QPPV, the PSMF and certain manufacturing sites need to be based in the EEA for a company to be able to market a medicine in the EU.

EMA is liaising directly with the marketing authorisation holders who either did not reply to the survey or have indicated in the survey that they do not plan to submit the changes required by 30 March 2019 and have manufacturing sites in the UK only, as this could potentially lead to supply disruptions.

EMA has analysed feedback from the survey and is now looking in detail at those medicines where there are risks of supply shortages and will assess how critical these are. As a regulator, EMA's role is to ensure that it has a complete overview of the potential risks, and to work together with the relevant marketing authorisation holders to address these risks as early as possible and discuss relevant mitigation measures.

EMA will also regularly monitor the submission of changes to marketing authorisations for all 694 products to check if the relevant variations/notifications are being submitted. Figures are likely to change as regulatory changes are submitted.

EMA urges those companies who have not yet informed EMA of their Brexit preparedness plans to do so as soon as possible to mitigate any risks to the continuous supply of medicines for human and veterinary use within the EU.

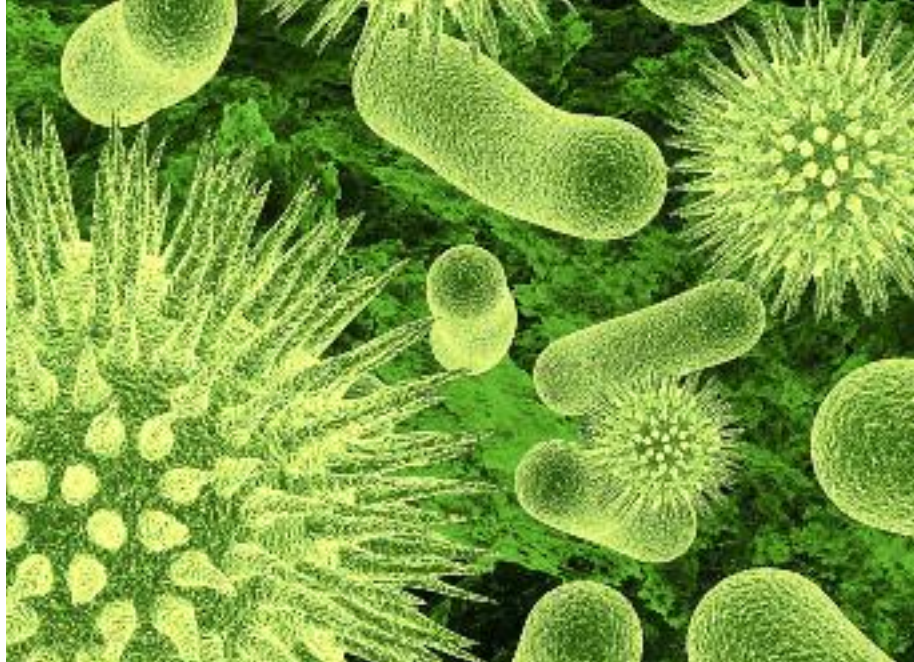
Companies are reminded to plan for the UK's withdrawal from the EU on 29 March 2019 and are advised to regularly check EMA's dedicated webpage on the consequences of the UK's withdrawal from the EU. In particular, EMA encourages companies to refer to the updated questions and answers and practical guidance for industry published on June 19, 2018.

## New medicine to treat infections caused by resistant bacteria

**September 21, 2018** – The EMA's CHMP has recommended granting a marketing authorisation for Vabomere (meropenem trihydrate/vaborbactam), a new treatment option against the following infections in adults:

- Complicated urinary tract infection, including pyelonephritis, a sudden and severe infection causing the kidneys to swell and which may permanently damage them,
- Complicated intra-abdominal infection,
- Hospital-acquired pneumonia, including ventilator associated pneumonia,
- Bacteria in the blood associated with any of the infections listed above,
- Infections due to aerobic Gram-negative organisms in adults with limited treatment options.

The lack of availability of medicines to treat patients with infections caused by resistant bacteria has become a major problem in recent years. It is estimated that at least 25,000 patients in the EU die each year from infections due to bacteria that are resistant to many medicines.



Vabomere is a fixed combination of vaborbactam, a new beta-lactamase inhibitor and meropenem, a broad-spectrum antibiotic belonging to the class of carbapenems that is already approved for use in the EU. It is a powder for concentrate for solution for infusion (drip into a vein).

Resistance to carbapenems has been increasing lately, in particular in Gram-negative bacteria, and is of major concern. Beta-lactamases are enzymes involved in bacterial resistance to these antibiotics. By inhibiting the action of beta-

lactamases, vaborbactam protects meropenem from being inactivated and restores its activity against many, but not all, carbapenem-resistant pathogens.

In the clinical development programme, the exposure to vaborbactam at the recommended dose was shown to be sufficient to protect the activity of meropenem against carbapenem-resistant Enterobacteriaceae. The CHMP also agreed that the studies did not indicate any major concerns regarding the safety profile of meropenem-vaborbactam.

## Gene therapy for rare inherited disorder causing vision loss recommended for approval

**September 21, 2018** – The EMA's CHMP has recommended granting a marketing authorisation for the gene therapy Luxturna (voretigene neparvovec), for the treatment of adults and children suffering from inherited retinal dystrophy caused by RPE65 gene mutations, a rare genetic disorder which causes vision loss and usually leads to blindness.

The mutations of the RPE65 gene, which encodes one of the enzymes involved in the biochemistry of light capture by the cells of the retina, hinder the patient's ability to detect light. It is a severely debilitating disease, characterised by a progressive loss of vision. Most patients will be blind by the time they are young adults. There is currently no treatment for this disease; support to patients is limited to measures

allowing the management of the disease such as aids for low vision.

Luxturna is meant for patients with confirmed biallelic mutations of the RPE65 gene (i.e., patients who have inherited the mutation from both parents) and who have sufficient viable retinal cells. It is the first gene therapy to be recommended for approval for a retinal disease. Luxturna works by delivering a functional

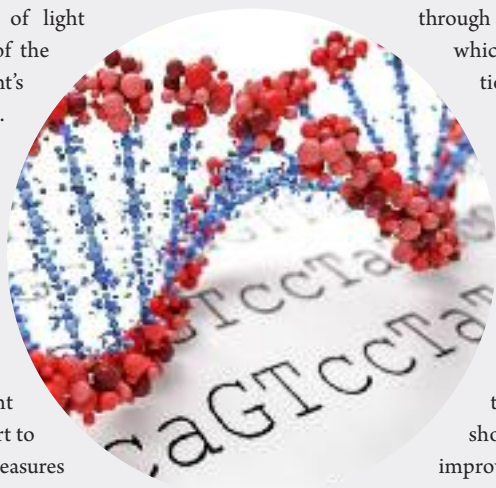
RPE65 gene into the cells of the retina through a single retinal injection, which restores the production pathway for the required enzyme thereby improving the patient's ability to detect light.

Luxturna was studied in 41 patients. In the main clinical trial supporting the approval of Luxturna, patients treated with the medicine showed a significant improvement of night vision,

one of the typical symptoms of the disease, after one year, while no improvement was seen in the control group. The most common side effects were conjunctival hyperaemia (eye redness), cataracts and increased intraocular pressure.

Given the novelty of the treatment and the limited number of treated patients, the CHMP requires the company to ensure the long-term follow-up of patients to confirm Luxturna's continuing efficacy and safety. Follow-up studies were agreed, including a post-authorisation safety study based on a disease registry in patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations, as well as a 15-year follow-up programme of efficacy and safety outcomes for all patients treated in the clinical programme.

The CHMP's opinion is based on the assessment by EMA's expert committee on Advanced Therapy Medicinal Products (ATMPs), the Committee for Advanced Therapies. Luxturna was designated as an orphan medicine and an ATMP and EMA provided protocol assistance to the applicant during the development of the medicine.



## EMA's proactive publication of clinical data: First report on transparency policy shows high user satisfaction

**July 16, 2018** – The EMA has published the first report on the implementation of its flagship policy on the publication of clinical data (Policy 0070). Under this policy citizens, including researchers and academics, can directly access thousands of pages from clinical reports submitted by pharmaceutical companies to EMA in the context of marketing authorisation applications for new medicines as of January 1, 2015. Clinical reports give information on the methods used and results of clinical trials conducted to demonstrate the safety and efficacy of medicines.

The report covers one year from the launch of EMA's clinical data website on October 20, 2016, and lists the 50 medicines for which clinical data were published, including orphan, paediatric, biosimilar and generic medicines, as well as the corresponding 54 regulatory dossiers. These data have attracted a total of 3,641 users, resulting in 22,164 document "views" and 80,537 "downloads" for non-commercial research purposes.

The report sheds light on the total number of documents published, the amount of commercially confidential information (CCI) redacted and the anonymisation techniques used. EMA accepted 24% of CCI redactions proposed by pharmaceutical companies, with the result that only 0.01% of 1.3 million pages published contained CCI redactions. The report also details the various anonymisation techniques used to protect personal data. It also suggests conducting a proper assessment of the impact of the anonymisation technique on data utility and improving the quality of the anonymisation reports.

The results of a user survey of the clinical data

website are also included in the report. Of the total respondents, 62% were affiliated to the pharmaceutical industry, 14% to academia, 8% were patients and 8% healthcare professionals. The report summarises the reasons of the different user groups for accessing the data and their views on its usability. Importantly, it shows that very few respondents disagree with EMA's rationale for developing the policy. In addition, most respondents strongly agree that publishing clinical data increases public trust in EMA's decision-making and that it allows the reassessment of clinical data.

To implement the policy successfully, EMA made sure that the pharmaceutical industry received regularly updated guidance. The Agency also provided one-on-one assistance to individual companies to prepare them for the publication of clinical data. As a result, EMA published an average of six dossiers a month in the period from October 2017 to May 2018, reaching the hundredth published dossier milestone on May 29, 2018.

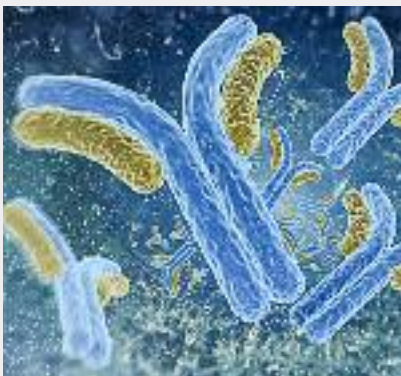
EMA is the first regulatory authority worldwide to provide open access to clinical data submitted by companies in support of their marketing authorisation applications. This is a cornerstone of EMA's commitment to openness and transparency, which was recently endorsed by the EU's General Court rulings on the limited scope of commercial confidentiality with regard to authorised medicines. Moreover, EMA's



proactive publication of clinical data has shaped the global debate towards more transparency, as other regulators, such as the US Food and Drug Administration and Health Canada, have subsequently implemented – or are considering implementing – similar transparency measures.

EMA is currently preparing for its relocation to the Netherlands, its new host Member State, and is implementing the next phase of its business continuity plan to facilitate the relocation. This will also impact the publication of clinical data as of the second half of 2018 and in 2019. EMA will liaise with pharmaceutical companies currently preparing their submissions. The Agency will do its utmost to resume this activity to the level outlined at the start of the policy once the relocation is complete.

## A monoclonal antibody for the prevention of migraine recommended for marketing authorisation



**September 21, 2018** – The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorisation for Emgality (galcanezumab), a monoclonal antibody for the prevention of migraine. Emgality belongs to a new class of medicines that work by blocking the activity of calcitonin gene-related peptide (CGRP), a molecule that is involved in migraine attacks.

It is estimated that approximately 15% of the population in the EU suffers from migraine. Patients experience recurrent episodes of intense,

throbbing headache, most often only on one side of the head. Sometimes, the pain is preceded by visual or sensory disturbances known as an 'aura'. Many people also experience nausea, vomiting and increased sensitivity to light or sound. Migraine can substantially impair a patient's ability to function physically, at work or school, and socially.

The exact cause of migraine is unknown, but it is believed to be a neurovascular disorder with disease mechanisms both within the brain and the blood vessels of the head. It is most frequent

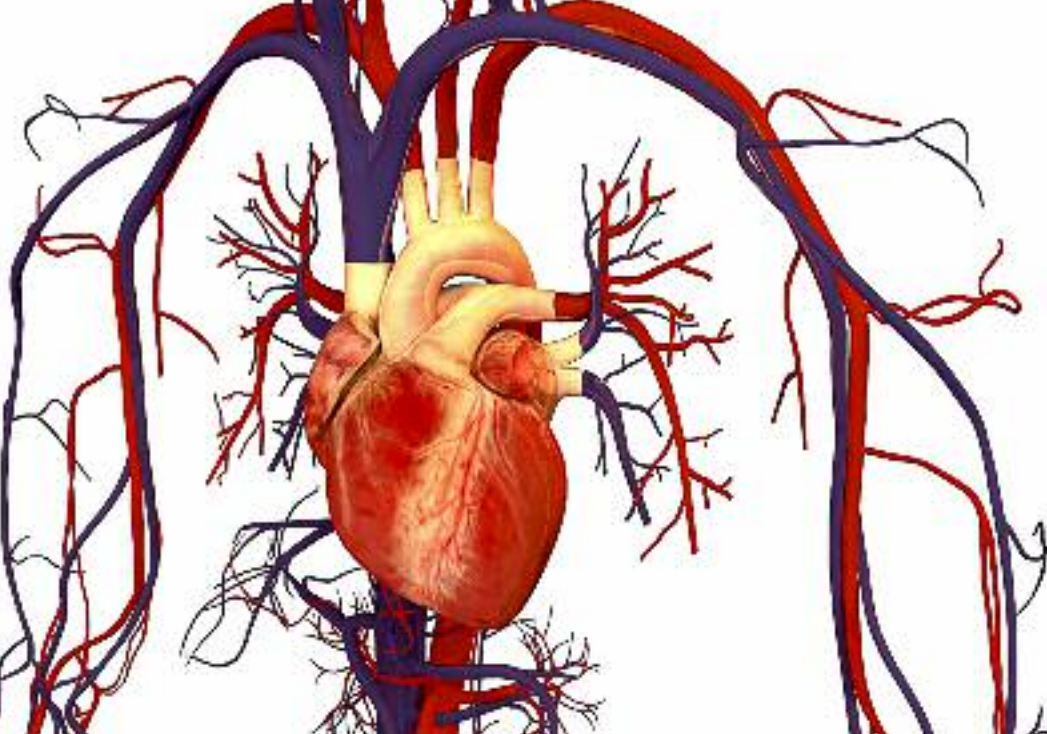


## Valsartan and sartan medicines: Review and risk assessment of impurities

**September 13, 21, and 28, 2018** – Valsartan is an angiotensin-II-receptor antagonist used to treat hypertension (high blood pressure), recent heart attack and heart failure. It is available on its own or in combination with other active substances. A review of valsartan medicines was triggered by the European Commission on 5 July 2018 to test the presence of certain carcinogenic impurities.

Initially, the review focussed on medicines containing the active substance manufactured by Zhejiang Huahai and Zhejiang Tianyu where unacceptable levels of Nnitrosodimethylamine (NDMA) were confirmed. A related impurity, Nnitrosodiethylamine (NDEA), was also detected in valsartan made by Zhejiang Huahai using its previous manufacturing process prior to 2012. Medicines containing valsartan from Zhejiang Huahai and Zhejiang Tianyu have been recalled and are no longer being distributed in the EU. An inspection by EU authorities in collaboration with European Directorate for the Quality of Medicines found that Zhejiang Huahai did not comply with good manufacturing practice in the manufacture of valsartan at the Chuannan site in Linhai, China. Consequently, this site is no longer authorised to produce valsartan (and its intermediates) for EU medicines. Marketing authorisation holders in the EU are prohibited from using valsartan from this site for the production of medicines. The inspection found several weaknesses at Zhejiang Huahai, including deficiencies in the way the company investigated the presence of NDMA and NDEA in its valsartan products.

Both NDMA and NDEA belong to the class of nitrosamines and are classified as probable



human carcinogens (substances that could cause cancer). How these impurities came to be present during the manufacture of sartans is yet to be fully established and is being evaluated in the ongoing review.

The EMA has now expanded its review of impurities in valsartan following the detection of very low levels of NDEA in another active substance, losartan, made by Hetero Labs in India. As a result of the detection of this impurity by German authorities, the review will now include medicines containing four other 'sartans' (angiotensin-II-receptor antagonists), namely candesartan, irbesartan, losartan and olmesartan. Like valsartan, these active substances have a specific ring structure (tetrazole) whose synthesis could potentially lead to the formation of impurities such as NDEA. The extension of the review to other sartans is precautionary.

EMA's risk assessment is based on the average levels of NDMA in the active substance produced by Zhejiang Huahai since 2012 (when the company changed its manufacturing process)

and on the assumption that all the NDMA is transferred to the final product. The life-time risk of cancer is considered low and is estimated to be in the order of 1 in 5,000 for an adult patient who had taken an affected valsartan medicine at the highest dose (320 mg) every day from July 2012 to July 2018. Patients who have taken treatments with lower doses or for shorter lengths of time will be at a lower risk. The risk will also be lower for patients who have taken valsartan produced by Zhejiang Tianyu, which had smaller amounts of NDMA than valsartan produced by Zhejiang Huahai.

Based on the trace amounts of NDEA seen so far in one batch of losartan from Hetero Labs, there is no immediate risk to patients. Patients are therefore advised not to stop taking losartan or other sartan medicines without speaking to their doctor.

Further tests are required to determine the extent of the contamination and whether impurities are present in sartan medicines above levels that can be considered acceptable.

in women and has a strong genetic component.

Emgality will be available as a solution for injection intended only for patients who have at least four migraine days per month. The benefits and safety of Emgality were studied in three pivotal trials involving 1,780 patients with episodic migraine and 1,117 with chronic migraine. After six months of treatment, patients with episodic migraine showed a reduction of 1.9 monthly migraine days on average compared to placebo. For patients with chronic migraine the reduction was 2 days. The most

common side effects are pain and reactions at the injection site, vertigo and constipation.

Emgality is the second monoclonal antibody therapy for the prevention of migraine to be recommended for authorisation, following the positive opinion for Aimovig (erenumab) in May 2018. There is no cure for migraine and these two medicines widen the therapeutic options for this disease. There are other available treatments to tackle the symptoms and reduce the frequency of migraine days. However, existing preventative treatments do not always

work well and may have unpleasant side effects.

The opinion adopted by the CHMP is an intermediary step on Emgality's path to patient access. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.

# Regulatory Matters



## Symbiotic relationships in medical writing and regulatory operations

SECTION EDITOR



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A symbiotic relationship is an “intimate interaction between two or more species, which may or may not be beneficial to either”.<sup>1</sup> We can think of the bee and flower relationship. The flower provides the bee with nectar, while the bee provides pollination. Each entity or group in the relationship benefits from knowing or interacting with one another; they need each other to survive and prosper.

The biopharma industry is a complex ecosystem with myriad interdependencies. The interconnected organisms in this ecosystem experience many moving parts within their respective operations, including shifting priorities/timelines, process changes, system upgrades, and internal/external requirements, just to name a few. This is evident on the micro- and macrocosm levels. Communication and collaborative interaction are the keys to a successful relationship, especially between a medical writing department and a document publishing/content management centre of excellence in regulatory operations. Creating a symbiotic relationship involves trust, collaboration, innovation, risk, people, and leadership.<sup>2</sup>

**Trust:** *Do you trust the expertise? Are you willing to share insights?*

Ensure expertise is in the right areas. Identify skills for each group and/or create subject matter experts. Ensure accountability. The focus of a document publishing and content management group is to provide documents that meet the electronic submission requirements. The group members are Word and PDF experts who focus on formatting, publishing, quality control, and submission readiness. We interact with medical writers, statisticians, and downstream submission publishers. It is important not to make one group responsible for work that can be done

by experts in another group. Each group can share and leverage their knowledge and expertise more broadly.

**Collaboration:** *Do you work cross-functionally? Do different groups come together?*

Promote the interaction of group members. Ensure all stakeholders are considered in the end-to-end timeline. Encourage representatives of the ecosystem to meet regularly and consult actively with project teams. The groups should have a general understanding of each other's role. Last-minute changes are known to happen in the clinical and regulatory space, and being able to identify the correct point of contact can save valuable time when compiling a submission.

**Innovation:** *Do you have processes to capture innovation? Can you learn to repeat them?*

Plan for success. Keep everyone up to date on process and procedure changes. Share across

groups what processes work and what doesn't work. Capture the best practices in order to repeat the desired outcome, then promote consistency. Part of my role is to meet with medical writers on a regular basis. We focus on quality metrics, concerns, issues, and processes. It is important that both groups participate. We are able to capture patterns, good and bad, and then implement a solution and/or perpetuate best practices.

**Risk:** *Can you afford to make the change? Does the benefit outweigh the risk?*

As mentioned before, our organisations have many moving parts and they need to synchronise across departmental boundaries. When a process or system requires an update in one area, we have to take time to investigate the impact within the ecosystem. If there is a symbiotic relationship, identifying the gaps to align the end-to-end process can become systematic and create opportunities for improvement across the organisations.

**People and leadership:** *Do we have the people involved to develop opportunity?*

Select people who can provide leadership. The ecosystem needs leaders who can prioritise projects or tasks then create a strategy and



execute it. Strategy is simple – focus on the activity. Execution is complex and takes time to perfect. “But without direction, simple clarity on strategy, execution is merely hysterical activity confusing effectiveness with activity”.<sup>3</sup>

The points above allow for knowledge transfer, gap identification, project prioritisation, and process and procedure consistency. The end goal is to ensure submission-ready components are delivered. All groups must interact in order to successfully meet deadlines.

The benefits of a symbiotic relationship can improve performance, increase effectiveness, expand workload, and outweigh risk with reward. Remember the bee and flower – only the flowers that interact with the bee prosper. The investment in the relationship determines the outcome; you get what you put in.

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# Regulatory Public Disclosure

## Editorial

Regulatory public disclosure (RPD) is a fast-evolving area. This regular section of *Medical Writing* and EMWA's RPD Special Interest Group (SIG) can help you develop your understanding and maintain your knowledge. The RPD SIG members' page: <https://www.emwa.org/members/special-interest-groups/regulatory-public-disclosure-sig/> has a new subpage for disclosure-related regulatory news updates: <https://www.emwa.org/members/special-interest-groups/regulatory-public-disclosure-sig/regulatory-news-emwa-newsblast/>.

In this issue's open-access RPD feature article (Meister R, page 57), a US-based colleague describes the historical background, development, and current status of the plain language summary. It raises awareness of the suitability of professional medical writers in conveying clinical trial outcomes to trial participants – and the wider general public – because we understand the clinical trial process and the importance of clinical trial transparency and disclosure, and because we can convey complex information with clarity. Writing plain language summaries is surely a work opportunity not to be missed.

Our short article this quarter is a slick “information harnessing” piece by Kathy B. Thomas, freelance consultant and regular speaker at EMWA conferences. Kathy generously shares her “go-to” internet sites hosting key clinical trial disclosure-related resources. Keep it handy for reference purposes.

Awareness of the importance of clinical trial disclosure is growing, as evidenced by increasing numbers of companies seeking to establish dedicated business units to uphold this new discipline. If you are involved in this swathe of development, and would like to write about it, do please contact me. As ever, send in ideas for articles, tips, and points to help us all hone our disclosure writing. I will continue to information share via this regular *Medical Writing* section, through [www.core-reference.org](http://www.core-reference.org) emails (sign up at: <http://www.core-reference.org/subscribe>), and through EMWA News Blasts.

Kind regards, Sam

## SECTION EDITOR



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## Clinical trial disclosure:

### Useful Internet sites for trial sponsors and database users

Clinical trial disclosure is a well-known topic to those performing and reporting clinical trials. Registration of new clinical trials and disclosure of results for completed clinical trials in public internet databases is now generally accepted by trial sponsors. Publications on the topic appear frequently in high-ranking journals, blogs, specialist newsletters, and general newspapers. Such publications report new or updated legal requirements, metrics of the reported (or *not reported*) information, and on the implications of the transparency and disclosure requirements for sponsors of clinical trials.

Information on the clinical trials can be found in internet databases (most freely accessible without any subscription). The databases are global, regional, or national, which makes the timely management, updating, and content consistency a challenge for those implementing and coordinating the database entries. Countries of the EU and of the European Economic Area (EEA: Iceland, Liechtenstein, and Norway) as well as the US are particularly active in advocating and enforcing clinical trial disclosure. Additionally, some further 40 countries worldwide have national disclosure obligations; certain countries have more than one relevant registry or database that needs attention.

Entry of information into the databases is based initially on the “Clinical trial protocol” – this constitutes the “registration” of a *new* clinical trial and later on, after the trial has been *completed* (... or prematurely ended) the database entry is based on “Clinical trial report” – a procedure that

represents the disclosure of clinical trial results (also referred to as posting of results).

#### USA

Clinical trials that are performed under the US jurisdiction and are applicable for disclosure are governed by the FDA Amendment Act of 2007 Section 801 (often referred to as FDAAA 801 statute), and which was expanded by the Final Rule making in 2016. The requirements of the statute, expanded by the Final Rule, are fully effective from 18 January 2017. The database associated with FDAAA 801 expanded by the Final Rule, is the ClinicalTrials.gov [www.clinicaltrials.gov](http://www.clinicaltrials.gov), which is maintained and managed by the National Institutes of Health (NIH), National Library of Medicine.

#### EU/EEA

For trials that are under the legal authority of the EU/EEA, the relevant law is the Regulation EU No. 536/2014, which is to replace the existing laws – namely the Clinical Trials Directive 2001/20/EC and the Paediatric Regulation (EC) No. 1901/2006. Regulation EU No. 536/2014 is intrinsically connected to a *functional* single EU portal and database.

Although Regulation EU No. 536/2014 came into force in 2014, its provisions will not take effect before mid 2020. This delay is due to complex technical demands of the single EU portal and database which will store and facilitate information flow between the EMA and EU/EEA member states. During the interim period (while the single portal and database are being developed, tested, and validated), the current applicable disclosure laws remain in force, i.e. the Clinical Trials Directive 2001/20/EC and the Paediatric Regulation (EC) No. 1901/2006. Consequently, the database that contains registration and results of clinical trials remains the [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu).

Despite the delay in the effective date for the Regulation EU No. 536/2014, sponsors of clinical trials in the EU/EEA are urged to invest time and resources to educate themselves and understand the requirements of Regulation EU No. 536/2014, assign staff and set up internally tested standard operating procedures, so as to be ready for the effective date.

#### Trial trackers

For the two ICH world regions that are the subject of this article, the databases are being monitored for timely entry of results of completed clinical trials. Outcome of such monitoring is performed with the so-called “trial



trackers” and the findings are public through live informatics tools that monitor compliance of the FDAAA 801/Final Rule-relevant trials in the NIH database (<http://fdaaa.trialstracker.net/>) and of trials in the EU/EEA, in the EudraCT database (<http://eu.trialstracker.net/>).

#### Facilitating learning and understanding of the clinical trial disclosure topic

The information presented in Table 1 below is intended to facilitate learning and understanding of the clinical trial disclosure topic. The Table contains information on the definitions of elements that are required for the registration and results disclosure of new trials or completed trials, respectively, in ClinicalTrials.gov and/or in the clinical trials register (EudraCT). As new topics are raised, the information on the Internet sites is updated.

The Internet sites with “frequently asked questions” (FAQs) provide valuable information on items raised by trial sponsors and database users. Other sites contain information about the procedures of how to enter the data into the database fields, definitions of fields, interpretations of the relevant laws or requirements from other influential bodies or organisations (such as the International Committee of Medical Journal Editors, the World Medical Association that developed the Declaration of Helsinki, and the World Health Organization).

#### Further information and references

Detailed information on the topic of clinical trial

disclosure is available in the recent publications and references within:

- Thomas Kathy B. Clinical trial disclosure and transparency: Regulation EU No. 536/2014. Public disclosure at the clinical trial level. *Medical Writing* 27(2):7–17, 2018 <http://journal.emwa.org/public-disclosure/clinical-trial-disclosure-and-transparency/> [accessed 2018 September].
- Thomas KB. Clinical trial disclosure and transparency: ongoing developments on the need to disclose clinical data. In *Medical writing the backbone of clinical development*. International Clinical Trials. pp 63-70, 2017. <http://edition.pagesuite-professional.co.uk/launch.aspx?eid=f6b80f6a-ddd6-4705-bc9a-8af003f96adb> [accessed 2018 September].
- Thomas KB. Clinical Trial Disclosure and Transparency: The Medical Writer’s Perspective; in Thomas KB, Reeves A, (eds): *EMWA Symposium*. EMWA, 2014, pp 6–17. <http://www.emwa.org/Documents/Transparency%20Symposium%20Budapest%20Final.pdf> [accessed 2018 September].

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**Table 1: Clinical trial disclosure: Useful sites for clinical trial sponsors and database users**

**US (ClinicalTrials.gov database) [www.clinicaltrials.gov](http://www.clinicaltrials.gov)**

FAQ NIH site	<a href="https://clinicaltrials.gov/ct2/manage-recs/faq">https://clinicaltrials.gov/ct2/manage-recs/faq</a>
Data elements and study registration requirements	<a href="https://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf">https://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf</a> Includes requirements from: WHO, ICMJE, and NIH
ClinicalTrials.gov <b>Protocol Registration</b> Data Element Definitions for Interventional and Observational Studies.	<a href="https://prsinfo.clinicaltrials.gov/definitions.html">https://prsinfo.clinicaltrials.gov/definitions.html</a> This site also contains information on individual participant data sharing (a requirement of ICMJE).
ClinicalTrials.gov <b>Results Data Element</b> Definitions for Interventional and Observational Studies	<a href="https://prsinfo.clinicaltrials.gov/results_definitions.html">https://prsinfo.clinicaltrials.gov/results_definitions.html</a>
Trial tracker	<a href="http://fdaaa.trialstracker.net/">http://fdaaa.trialstracker.net/</a>

**European Medicines Agency (EMA) [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)**

FAQ EMA site	<a href="https://eudract.ema.europa.eu/docs/guidance/EudraCT%20FAQ_for%20publication.pdf">https://eudract.ema.europa.eu/docs/guidance/EudraCT%20FAQ_for%20publication.pdf</a>
EudraCT Database	<a href="https://eudract.ema.europa.eu/help/Default.htm">https://eudract.ema.europa.eu/help/Default.htm</a> site also includes links to: ● Protocol-related information ● Result-related information
Clinical Trials Regulation (EU) NO 536/2014 Q&A (Version 1.0 April 2018)	<a href="https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf">https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf</a>
Community clinical trial public home page	<a href="https://eudract.ema.europa.eu/">https://eudract.ema.europa.eu/</a> site also includes links to: ● Protocol-related documentation ● Result-related documentation ● Training tutorials on results entry into database ● Statistics ● Technical aspects
Trial tracker	<a href="http://eu.trialstracker.net/">http://eu.trialstracker.net/</a>

EMA=European Medicines Agency; EudraCT= European Union Drug Regulating Authorities Clinical Trials; ICMJE=International Committee of Medical Journal Editors; NIH=National Institute of Health; WHO=World Health Organization

**CORE Reference**



- Read the CORE Reference Press Release on the TransCelerate CSR template at: <https://www.core-reference.org/news-summaries/core-reference-statement-on-transcelerate-csr-template/>
- CORE Reference (available for download from <http://www.core-reference.org/core-reference/>) identifies each point in an ICH E3-compliant clinical study report where

anonymisation considerations should apply. Downloads stand at 15,000+ (December 2018).

- Sign up for emails via: <http://www.core-reference.org/subscribe>.
- CORE Reference-related updates are now available in Japanese on a dedicated blog (<https://clinos.com/blog/category/core-reference/>). Thank you to Yukie Uchiyama

(responsible for Japanese writing of the blog) and Hiroko Ebina (responsible for quality assurance of the blog) for making this initiative possible. Note: The opinions expressed in Yukie Uchiyama's blog, and the interpretations of CORE Reference are solely those of the blogger, and are not necessarily those of the CORE Reference authors.

## Status updates – from regulatory regions

### United States

1. In September 2018, FDA issued draft guidance titled “Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank”

(<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM607698.pdf>) describing FDA thinking on financial penalties against sponsors of clinical trials who do not register and/or submit results information to ClinicalTrials.gov.

2. Clinical study protocols are publicly disclosed documents, making the following September 2018 draft FDA guidance releases on protocol development relevant:

- “Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics – Guidance for Industry” (<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621817.pdf>)
- “Adaptive Designs for Clinical Trials of Drugs and Biologics – Guidance for Industry” (<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm201790.pdf>)

### Europe

1. EMA has a new “Clinical data publication” page (<https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication>) that explains that EMA is temporarily suspending clinical data publication until further notice.

This page also includes links to:

- The “**Support for industry on clinical data publication**” page (<https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication/support-industry-clinical-data-publication>) This comprehen-

sive page includes detailed guidance for pharmaceutical companies on requirements to comply with Policy 0070, and also includes downloadable justification table templates.

- **EMA’s clinical data website** (<https://clinicaldata.ema.europa.eu/web/cdp/home>) This page hosts publicly disclosed clinical data.
- The “**External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use**” page (<https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication/support-industry-external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data>).

The latest implementation guidance is Revision 4, dated November 9, 2018; ([https://www.ema.europa.eu/documents/regulatory-procedural-guideline/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data\\_en-3.pdf](https://www.ema.europa.eu/documents/regulatory-procedural-guideline/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data_en-3.pdf)) read the summary of changes at: [https://www.ema.europa.eu/documents/other/summary-changes-external-guidance-implementation-european-medicines-agency-policy-publication\\_en-2.pdf](https://www.ema.europa.eu/documents/other/summary-changes-external-guidance-implementation-european-medicines-agency-policy-publication_en-2.pdf).

2. EMA is compiling a report listing those sponsors on EudraCT who are not compliant with results posting requirements. The report was planned for publication in September 2018 and EMA will be contacting those sponsors individually. This information was communicated directly by an EMA representative at a web meeting of the DIA’s Clinical Trial Disclosure Community in mid September 2018.

3. EudraCT Clinical Trials Tracker (<http://eu.trialstracker.net>) is fully established. This tool is searchable by sponsor and indicates

the percentage of reported trials on EudraCT – out of the trials that are due to report.

4. In September 2018, 11 national research funding organisations, backed by the EC and the European Research Council (ERC), announced the launch of “cOAlition S” (<https://www.scienceurope.org/coalition-s/>), an initiative to make full and immediate open access to research publications a reality.

By January 1, 2020, the aim is to fulfil this main principle: “By 2020 scientific publications that result from research funded by public grants provided by participating national and European research councils and funding bodies, must be published in compliant open access journals or on compliant open access platforms.”

### ... from the Journals

The 2018 *BMJ* article: “Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource” (<https://doi.org/10.1136/bmj.k3218>) describes compliance of 50% for results posting on EudraCT over a 1-year period to December 21, 2016. This paper also describes the EudraCT Clinical Trials Tracker (<http://eu.trialstracker.net>).

Hopkins and colleagues’ September 2018 paper “Data sharing from pharmaceutical industry sponsored clinical studies: audit of data availability” (<https://doi.org/10.1186/s12916-018-1154-z>) assesses whether data sharing policies are facilitating independent researcher access to participant-level data from industry-sponsored trials 2 years after publication of the primary results. The findings show that there remains significant room for improvement; the authors present key issues that have limited data sharing.

## Resources

### November 2018 TransCelerate assets: New CSR, new SAP, and updated CSP Templates

TransCelerate has released new and updated clinical document templates under their Common Protocol Template resources at: <http://www.transceleratebiopharmainc.com/assets/common-protocol-template/>

Read the CORE Reference Press Release on the TransCelerate CSR template at:

<https://www.core-reference.org/news-summaries/core-reference-statement-on-transcelerate-csr-template/>

### TransCelerate webinar on the Common Protocol Template

A recording of the September 27, 2018, TransCelerate webinar session on their Common Protocol Template, along with a PDF slide deck is available from: <https://connect.eventtia.com/en/dmz/4d19/> website

### EFPIA-sponsored Data Transparency Conference – Brussels, February 2019

### On February 12 and 13, 2019, the ECCRT Data Transparency Conference

(<http://www.eccrt.com/events/eccrt-data-transparency-conference>) on “Demystifying Clinical Data Transparency: Lessons learnt so far” includes speakers from the CORE Reference development team. Programme: [http://www.eccrt.com/sites/default/files/eccrt\\_images/data\\_transparency\\_conference\\_eccrt.pdf](http://www.eccrt.com/sites/default/files/eccrt_images/data_transparency_conference_eccrt.pdf)

# Medical Communication

## Help reviewers tell you what they want

### SECTION EDITOR



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### Editorial

#### Dear all,

In a follow-up to the excellent article from Douglas Fiebig on how to use your review cycle effectively, this issue presents an extremely insightful article from Diana Radovan on how to help reviewers to communicate better with writers. Diana has more than 10 years' experience in clinical development and scientific research, including preparation of regulatory documents and scientific publications. She has worked on both the client and vendor sides of the equation and so offers us her unique perspective on the writer/reviewer relationship.

In her article, Diana outlines the issues with poor communication between writers and reviewers, and how misunderstandings can have a dire effect on the quality of a document. She also gives many tips and tricks to help avoid problems in the first place, and her article is packed with incredibly useful tables, tools, and checklists for writers to use. I consider them an early Christmas present (thanks Diana!) and have already printed many out and will be sticking them on my office wall!

As 2018 draws to a close, I hope that it has been a good year for you all. Enjoy the upcoming Christmas break – may your socks stay snowball-proof and may Santa be kind.

See you in 2019!

Bestest,  
**Lisa**

### Introduction

Review is an integral part of the medical writing process and relies on clear communication between the medical writer and the reviewer(s). This is a two-way street. Review can be a frustrating process for both the writer and the reviewer(s) when there is miscommunication.

Thus, both parties are responsible for ensuring that the review process runs as smoothly and efficiently as possible. Ultimately, there is no “us” and “them” in the document development process, but a common goal to be reached by a team within a clearly defined timeframe: finalising fit-for-purpose documents for submission to health authorities, which will ideally result in a successful marketing authorisation approval.

My aim in this article is to give us writers hands-on tools for improving the communication with our reviewers, by making our review expectations more clear. I am presenting specific, simple principles that reviewers can practice throughout the document review process until they become habitual, including examples of how to provide comments that are unambiguous, actionable, and relevant.

### What review is and isn't (or at least shouldn't be)

Review is a process conducted at different stages of document development, to ensure that a document meets its purpose, i.e., that it is complete, coherent, and aligned both with the overall strategy of a specific project and the expectations of the intended ultimate audience, which for regulatory documents – is always the health authority (not the manager of a certain reviewer!).

Review differs from quality control (QC) in many aspects. Review should not be a check of numbers, spelling, and company-specific Style Guide conventions. Ensuring that these aspects are met falls under the responsibility of the medical writer throughout all document development stages, and of QC specialists and document managers/document administrators at later stages; such responsibilities are usually defined by a company's standard operating procedures (SOPs).

While it is often easier for reviewers to check abbreviation lists, fix spelling errors, and propose taste-driven linguistic changes on already linguistically correct text,<sup>1</sup> what we ultimately want as medical writers from our reviewers is something else: constructive, unambiguous, and timely strategic input (“strategic review”), primarily on document sections relevant for each reviewer's functional role (“function-driven review”) and on each document, considering both the document type (“eCTD placement-driven review”, based on its place/purpose within the electronic common technical document [eCTD]) and the document development stage (“staged review”).

### Reviews are sometimes poor, but we can change this

Several studies have shown that inefficient reviews are not uncommon across the pharmaceutical industry. Throughout several review rounds, the reviewers were asked to categorise their own comments on a specific document into one of the following categories: rhetorical (content-related/strategic), editorial, and stylistic; they assessed their comments as largely rhetorical. When the consultants looked at the drafts and categorised comments based on more objective criteria than personal opinion, they found that the vast majority were in fact editorial and stylistic, even on advanced drafts of the document.<sup>2,3</sup> The question is: why? Various reasons account for the often ineffective and inefficient review process seen across the industry, most of which are largely unintentional and can be at least partially corrected with appropriate training.

We should not forget that reviewers aren't primarily reviewers; they have been trained to be experts in their field (for example, statistics, bioanalytics, or clinical research), not communicators. While exercising their role in a pharmaceutical company, they wear many hats, and the “reviewer” hat is just one of them. Often they could even be quite frustrated that the medical writer and other reviewers do not understand what they want. After all, their comment was quite clear!

Some reviewers do not have a clear



understanding of how their review needs to change based on document type or document development stage, especially in companies that do not provide sufficient training on the eCTD structure during the initial onboarding phase. A reviewer will often approach a document with the same “strategy”, regardless of whether this document is, for example, a clinical study report (CSR), a summary of clinical safety (SCS), or a clinical overview (CO), reading it page by page, largely focusing on things like abbreviations and spelling, and gradually reducing the number of his/her comments by the time he/she gets to the results and conclusions sections.

In short, the expectations and objectives of the review are more often than not unclear for reviewers, although medical writers may think otherwise. It is up to us medical writers to recognise such issues and train our reviewers without sounding patronising. In 2015, Douglas Fiebig<sup>1</sup> laid down the “six vital ingredients” for how to ensure a great review process across multiple cycles:

- Define a structured review process
- Use a collaborative review tool, such as PleaseReview
- Clarify review expectations
- Implement staged reviews
- Plan review as a defined activity
- Enforce the review process

I have worked in different pharmaceutical

companies and also on the vendor side. Therefore, I’m very aware that the medical writer’s role is defined differently in different institutions, and I’d advise you to always raise awareness about the role played by medical writers in developing documents and in the industry in general, and to clarify the responsibilities of all parties involved, even if these are already covered by an SOP.

For us medical writers it may be obvious that in addition to writing, we not only manage comments but also act as mediators in case of conflicting strategic timelines, bringing discussions back on track during meetings and making sure that comments are kept. In line with this, we do not bring all comments provided on a draft to a comments resolution meeting (CRM), but only critical and at times conflicting comments from different reviewers. Keep in mind that some reviewers may have either worked with medical writers in a different set-up in another company (and therefore have very different expectations from us than we assume) or may have never even heard the wording “medical writer” before, especially if they are new in their role in the pharmaceutical industry.

If a reviewer is, for example, working on a submission for the first time (even if he or she does not wish to openly acknowledge this), an experienced medical writer can also be a resource for regulatory guidance, eCTD structure basics,

and roles of different team members during document development, beyond what is already covered in sometimes multiple and lengthy SOPs. A kick-off meeting for every writing project is a good starting point to set such things straight.

The aspects and tools that I provide below (and in particular the tabular presentations) could be introduced at the kick-off meeting with each clinical team you work with, but it is also a good idea to incorporate them in routine cross-functional trainings, to be held both during the onboarding phase and as refresher trainings, at least once a year within a given organisation. In addition, laminated hand-outs with key principles and specific examples are always useful at the end of such trainings. The reviewers can keep them on their desk and use them on a daily basis while conducting reviews.

Last but not least, when we mentor junior medical writers and review their documents, we should of course also adhere to the same principles. It is up to each and all of us medical writers to create, enforce, and maintain good writing and review practices across the industry.

## The Responsible Reviewer’s Checklist

Consider introducing reviewers within your organisation or at the client’s site to a tool that I like to call “The Responsible Reviewer’s Checklist” (Table 1).



**Table 1. The Responsible Reviewer's Checklist**

**Before review**

- 1 Get familiar with the **eCTD structure, SOPs, and relevant regulatory guidelines**. Put yourself in the shoes of the **ultimate target audience (health authority for regulatory documents)**. They need to make a yes/no decision, rather than be educated. With this in mind: what do they require to know?
- 2 Get familiar with the **source data** (CSP, SAP, CRF, TFLs, etc.) and **do not ask for changes that can no longer be implemented after DBL** (e.g., in primary analysis, additional sensitivity analysis after second draft CSR review etc. close to submission deadline, adding data not in the database etc.).
- 3 Get familiar with the **electronic review tool(s)** used (**document management system**, e.g. *Documentum* or **collaborative review tool**, e.g. *PleaseReview*) and use its/their capabilities.
- 4 Once you have agreed on timelines, **make yourself available. Plan time ahead** (in your Outlook calendar; ask your PA for support). **Delegate** your review if you know you will be away on vacation and guide your back-up through the basics of the project and review expectations before your vacation. **Inform the medical writer** of your absence and contact details of your representative.

**During review**

- 5 **Focus on:**
  - **providing input on relevant sections for your functional role/area of expertise**, keeping in mind the **document type** (based on its place in the eCTD structure) and **document development stage**
  - **providing strategic input on content** in the form of **specific, actionable, and relevant** comments<sup>a</sup>
  - **categorising your comments** into: *major-critical, minor-not critical; cosmetic*; avoid wordsmithing based on personal taste and checking abbreviations or numbers in programmed in-text tables.

**During the CRM**

- 6 **Come prepared to the CRM:**
  - **consider** other reviewer's **comments**
  - **propose** pragmatic **solutions** (ensure a balance between the required content and the target submission date), especially for critical comments that may require a change in strategy or additional analysis; consider whether this comment is truly critical at this particular stage.

**After the CRM<sup>a</sup>**

- 7 **Offer support to the medical writer** in addressing any remaining challenging comments if needed.

CRF = case report form; CRM = comments resolution meeting; CSP = clinical study protocol; CSR = clinical study report; PA = personal assistant; SAP = statistical analysis plan; TFLs = tables, figures, and listings;

<sup>a</sup> The review cycle continues and steps 1-7 are repeated for the next stages, until document finalisation.

**Table 2. Focus of review by functional role/area of expertise (function-driven review)**

Role	Focus
Clinical expert	Medical background/unmet medical need Clinical interpretation and relevance of results Overall consistency of messaging across sections and clinical programme Benefit-risk assessment
Statistician	Description of statistical methods and statistical interpretation of endpoints
Regulatory affairs manager	Adherence to regulatory guidelines specific for the respective class of drug and therapeutic area; addressing regulatory feedback received throughout the clinical development programme (on study design, safety etc.), if applicable
Clinical pharmacologist	Pharmacology methods and results
Clinical study manager	Description of study conduct
Bioanalytical expert	Description of bioanalytical methods
Senior management	Alignment of key messaging with overall product and company strategy

In addition to including it in trainings, I would also suggest attaching it as a pdf when initiating review cycles, and whenever you send a document for review to senior management, either directly or through someone else (e.g. medical/

clinical expert, regulatory affairs manager, or the senior manager's personal assistant [PA]).

Senior managers are unlikely to attend your trainings, but will at least be informed of your expectations, and you might end up being

positively surprised with the results of this exercise. Also talk to their PA well in advance to set aside time in their calendar.

Overall, this tool can be an effective way to create a common understanding within a

**Table 3. Focus of review by document type (eCTD placement-driven review)**

Document type	Purpose within eCTD <sup>a</sup>	Focus
CSR [4, 5]	Reports methods applied in an individual clinical study and clinical study results [4,5]	How the study was conducted and how results are reported at individual study level; most detailed clinical data presentation
SCS/Module 2.7.4	Summarises safety data relevant for a particular regulatory submission [6]	How safety is summarised across studies (usually in safety poolings); intermediate level of detail
CO/Module 2.5	Is a critical appraisal of the data in a clinical submission; it provides the clinical context of the data and a benefit-risk assessment that should ultimately support the proposed label [6]	How results are critically evaluated in support of the proposed label; benefit-risk assessment is essential and should be supported by the rest of the document and aligned with the SmPC, USPI, and RMP; data are not presented again at the same level of detail as in individual CSRs and summary documents, but critically assessed

CO = clinical overview; CSR = clinical study report; RMP = risk-management plan; SCS = summary of clinical safety; SmPC = summary of product characteristics; USPI = United States Prescribing Information.  
<sup>a</sup> in the world of electronic submissions (as most submissions tend to be nowadays), reference documents are just one click away in the electronic Common Technical Document structure.

**Table 4. Focus of review by document development stage (staged review)**

Document development stage	Focus
Shell	The methodology is complete and accurately described. The data presentation strategy is defined and fit for the purpose of this specific document (considering the class of drug, therapeutic area, and eCTD location). <ul style="list-style-type: none"> <li>● The use of tables vs. text is agreed upon within the team and found to be adequate.</li> <li>● The inclusion of endpoints is accurate and complete.</li> <li>● The key conclusions matching the primary and secondary objectives of the study will be supported by the data shells.</li> </ul>
First draft	The interpretation of the data is correct. The document is complete (everything needed is in, nothing is missing).
Second draft	First draft comments have been appropriately addressed. Key messages are clear and consistent within the document and across the entire project (not only on the clinical level, but also consistent with pre-clinical data).
Final draft	High-level messaging adequately supports overall project filing strategy.
Final version	The document is fit for purpose.

eCTD = electronic common technical document

document development team of what the review process entails.

### Focus, focus, focus!

The need for a focused review may seem obvious, but I have nonetheless very often seen statisticians “improving” document wording based on personal taste (and thereby at times changing the meaning of a sentence that was once correct ...), clinical experts checking the list of abbreviations rather than focusing on the clinical interpretation of data, regulatory affairs managers adding two spaces instead of one after each full stop throughout an entire document (while ignoring company-specific style conventions), and the list could go on.

I am sure that all of us have had such



experiences with different teams and we can all agree that this is not the kind of feedback we wish to receive throughout the review cycles

of a document with tight timelines to be met and critical data to be interpreted. It is both ineffective and inefficient.

**Table 5. Why some comments are ineffective and how to provide better comments**

Usual comment	Why the comment is not helpful and how to improve it	Better comment
“Can we align this with our recent project X?”	The writer may not have worked on this older submission. Moreover, is the request to specifically align a sentence, a paragraph, or to use a similar table? The writer may not know what is being asked. If it is just one sentence that you want used as a prototype, look it up yourself and provide it directly during review.	“Please describe serious infection results as follows: ‘Patients treated with drug X are not at a higher risk of developing serious infections than patients treated with drug Y.’”
“This is bad.” [1]	What is bad? The writer cannot know what is bad (a word, a sentence, a paragraph, the whole document) and how to improve it. Provide an alternative.	“Please reword this sentence to x and y because...” Include a reason for your request.
“What about allergic reactions?”	It is not specific and not actionable. The level of intended detail is not specified. There are different ways of presenting such results. For the writer to address this comment, a discussion is required. Check the data yourself and consider their key message, then propose a specific data presentation strategy and wording.	“Please present allergic reactions in tabular format by treatment group.” or “Please add ‘Allergic reactions were reported in 1%-2% of the patients in each treatment groups.’ (I have already checked the data myself).”
“Refer to Figure 8 and place in context.”	The writer can easily add a reference but “place in context” does not provide the content that the reviewer would like to see added. Clarifying the regulatory or clinical context in specific wording would help in this case.	“Please add: ‘... as described in Figure 8. This result is particularly relevant for patients with advanced disease X who do not respond to standard first line therapy with drug Y.’”
“Should we use the word <i>inhibitor</i> or <i>antagonist</i> ?”	It is a question; quite likely, it has been asked before within the same team, for the same document, and the discussion is becoming redundant. Make a proposal.	“Please use <i>antagonist</i> throughout the document and use it consistently across this clinical programme.”
“Can we add more information on cardiovascular events?”	Usually the answer would be: “Yes, we can (if we have the data)”. But what to add? Only serious events? Only fatal ones? A table? Or only text? Or information on those events leading to discontinuation? This kind of comment shows that the reviewer did not make the effort to look at the data and to think of what needs to be added with priority. Make comment more accurate.	“Please add frequencies of patients reported with serious cardiac events by treatment groups, then add “No clinically relevant differences were seen among groups.” (I have already checked this; reference: Table 15.3.4.5).”
“Why aren’t you presenting haematocrit values?”	“I didn’t want to” could be the answer. The comment does not specify if values should be presented as table or text, i.e. the key message of these data is missing. It is also not clear why singling out this lab parameter is considered relevant. Leave no doubt about what you want and propose specific wording to be added.	“There’s a concern of a drop in haematocrit values with this type of drug. Thus, please add: ‘Unlike with other inhibitors of class X, no decreases from mean baseline values were seen in this study (Table 15.3.10.2).’”

My experience is that teams need to be reminded of what to focus on, based on their function, document type, and document development stage. Last but not least, some reviewers tend to lose track of the ultimate audience of regulatory documents (the health authority!), and instead anxiously focus on how their line manager will perceive their review. As medical writers, it is part of our job to bring reviewers back on track and remind them of what to focus on (Tables 2–4).

Somewhere around the time of the final draft

(e.g. after second draft review), the QC step will take place. Inform your reviewers, as applicable at each draft stage, that the document has/has not yet been QC-ed. The second or final draft is usually also reviewed by Senior Management and/or the Principal/Coordinating Investigator. Other reviewers, such as Key Opinion Leaders, may also be involved at this stage. At CRMs, reviewers belonging to the core clinical team need to be ready to tackle any challenging, strategic, conflicting comments coming from these additional reviewers. Medical writers

should remind core team members of that, and potentially also ask them to align with their functional line managers early on, to avoid very late surprises (to the extent realistically possible).

### Train reviewers on how to make their comments more specific

Providing good comments takes substantial time during review, but will avoid a lot of confusion within the team later. Learning how to provide good comments also takes time, but once this has

been learnt and applied, it pays off for everyone involved in the development of a document. The reviewer is required to take one step forward and not only identify a problem (by simply criticising: “This is bad”), but also provide a solution.

This requires both some thinking and often even digging into the data, however this is the only way in which a review is actually “complete”, although a reviewer e-mailing you saying “I have completed my review” may have thought otherwise. Without a proper and truly complete review, the review process does not add much value, it uses time and resources, and makes us medical writers feel like we are pulling teeth at CRMs.

Replacing broad questions with specific answers and clear rewording suggestions pays off, but we need to train our reviewers and put them in the shoes of those receiving poor comments, clearly showing them why their comments aren’t as clear as they may think (Table 5).

As medical writers, it is up to us to give reviewers the opportunity to see how it feels to be at the receiving end of poor comments, and make them think and practice (after providing them with guiding principles) how to better word comments. As a rule of thumb, comments should be:

- **Specific and constructive:** “This is bad” written on the front page of a document does not indicate what is bad and does not help the team move forward and improve the document; pointing out specifics of what is bad and suggestions on how to “correct” the bad part does.
- **Actionable:** using an action verb (“Add/write/refer to x, y, z”), not an open question (“What about adverse events?” or “Why didn’t you describe adverse events?”, to which the writer may think “Aha, yes, What about them?” or “Because I didn’t want to.”) is always better.
- **Relevant:** reviewers should consider the timing and relevance of their comment before asking for a major change that would either completely change the structure or is too late (keeping the target submission timeline in mind) to address (e.g., we cannot redefine the primary analysis of a study post-hoc [after database lock]); there is a difference between a “nice to have” comment and a “critical” one [a must for the team to consider and discuss]).

It is essential that we are clear about what we want and how we want it done. We medical writers should clarify what we want the reviewers to focus on and how comments should be provided, ideally well ahead of the start of the review process, i.e. at the kick-off meeting. If reviewers understand what is being asked of them, those of us wearing the medical-writing hats will hopefully receive comments that are easy to implement and do not require endless discussion at CRMs.

## Conclusions

Nobody is born a reviewer. Review is a skill that can be taught and learnt. As professional medical writers and communication experts, we should take the time to train our teams both on our and on their responsibilities when it comes to document development, not all of which can be covered by an SOP. In particular, we should train them on how to provide clear, specific, constructive, actionable, and relevant comments, thereby helping each team member meet his/her full “reviewer potential”. Everyone involved in the development of a document will benefit from this, which will not only ensure a smooth collaboration, but ultimately will save the pharmaceutical company as a whole both time and money. Having the reviewers adhere to basic, clearly laid out principles when they conduct their review, aligned with their functional role, document type, and review stage, should improve the efficiency and effectiveness of the review process throughout clinical development and across organisations.

## Acknowledgements

I would like to thank Lisa Chamberlain James for reading an earlier version of this article and for her valuable feedback.

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# Medical Devices

## Patient-reported outcomes for medical devices

The good news first: Patient-reported outcomes (PRO) are basically the same in both the medical device and the pharmaceutical sectors. There are the general quality of life tools such as the EQ-5D<sup>1</sup> or the Short-Form Survey questionnaires (e.g. SF-12, SF-36),<sup>2</sup> and there are tools that target specific disease areas, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ)<sup>3</sup> and the Oswestry Disability Index (ODI).<sup>4</sup>

The most commonly used PRO in the medical device sector is the EQ-5D questionnaire because it is easy to use, comprising five questions and a visual analogue scale. It is one of the cheapest questionnaires (yes, cost plays a role in medical devices, particularly if you want to convince somebody to use PRO) and can be used to determine quality-adjusted life years (QALY).

### Use of patient-reported outcomes

PRO are important tools to measure patients' experience with medical devices and the effects of treatment. PRO complement clinical and physiological information and can be used as clinical and physiological endpoints. For instance, in trials with rare complications, quantifying a patient's health status may be a critical requirement for assessing treatment benefits.<sup>5,6</sup> Furthermore, PRO are relevant as they represent the patient's voice.<sup>6</sup>

It goes without saying that the quality of life after a procedure is important; it is not enough to survive a treatment only to be left with intolerable symptoms. For example, it is undesirable to have a successful procedure only to suffer a disabling stroke. On the other hand, a therapy might not increase survival but might improve the quality of life. For instance, in trials in peripheral artery disease or of orthopaedic devices, pain reduction is highly relevant and can be measured with PRO, e.g. Wong-Baker Faces<sup>®</sup> Pain Rating Scale<sup>7</sup> or the Visual Analogue Scale (VAS).<sup>6</sup>

Measuring quality of life in combination with survival is the concept of QALYs. QALYs are relevant when calculating the incremental cost-effectiveness ratio (ICER).<sup>8</sup> The ICER is

calculated as the difference in costs between two possible interventions divided by the difference in their effect. A common application is in cost-utility analysis. Having set a threshold for cost-per-QALY, it can be used to determine which interventions to adopt. Thresholds vary among countries, but in the UK, NICE typically has a threshold of between £20,000 and £30,000 per QALY.<sup>9,10</sup>

### Relevance of patient-reported outcomes

PRO have been used increasingly over the years<sup>6</sup> and it is expected that their relevance will continue to rise. New consensus documents on clinical trial endpoints now recommend use of quality of life endpoints: endpoint definitions now include PRO in coronary intervention trials<sup>5</sup> and transcatheter mitral valve trials, where improvement in quality-of-life, e.g. KCCQ improvement by  $\geq 10$ , is part of the patient success endpoint.<sup>11</sup>

This summary is intended to give a broad overview of the use of PRO in the medical device sector. In a nutshell, PRO are relevant and are used in the same way in both the medical device and pharmaceutical industries; therefore medical device writers are encouraged to read the full issue of *Medical Writing* on PRO. Happy reading!

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# Journal Watch

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

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## Are treatment effects significantly larger in trials published in a language other than English?

*Annals of Internal Medicine* published an excellent research article on the association between treatment effect estimates and publication characteristics.<sup>1</sup> Researchers from France and Germany (Academic hospitals and the Cochrane Centre) – and funded by Cochrane France – conducted the meta-epidemiologic study.

The objective was to compare treatment effects between published and unpublished randomised controlled trials (RCTs) and between trials published in English and other languages. They analysed 5659 RCTs included in 698 meta-analyses, and the study selection was well done, including data from Cochrane reviews published between March 2011 and January 2017, as well as trial references cited in the reviews. The study Included 356 unpublished trials and an additional 393 in a language other than English.

Treatment effects were larger in published trials rather than unpublished RCTs (combined ratio of odds ratios [ROR] for 174 meta-analysis, 0.90 with 95% CI, 0.82 to 0.98). Treatment effects were also larger for trials published in a language other than English. (combined ROR for 147 meta-analysis, 0.86 with 95% CI, 0.78 to 0.95).

These results confirm that restricting a search to published trials may lead to overestimation of treatment effects, possibly affecting meta-analysis results and conclusions. The study questions the recommendation to consider all languages in systematic reviews. There is language bias, as trials published in a language other than English showed larger treatment effect estimates than those published in English.

Are results of RCTs only published in English more reliable than RCTs in a non-English language?



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estimates: A meta-epidemiologic study. *Ann Intern Med.* 2018;169:385–93.

## Certain European countries underperforming in cancer research relative to their GDP



A team of British researchers published a bibliometric analysis of European cancer research papers listed in the Web of Science index from 2002 to 2013 with the objective of quantifying research activity in 28 European Union (EU) member states, along with Iceland, Norway, and Switzerland (EU31). Data on disease burden were obtained from the World Health Organization. Papers were analysed by cancer anatomical and research domains. Sources of financial support (2009–2013) were searched. Country Gross Domestic Product (GDP) data

were used to contextualise the findings. There are limits to such a bibliometric search, which includes only published data, without appraising the quality of the research papers, nor the amount of funding per research paper. The main observations were:

- Cancer research papers from EU31 correlated well with national GDP ( $r^2 = 0.94$ ).
- Certain cancer sites (lung, oesophagus, and pancreas) were under-researched relative to their increasing disease burden and poor prognosis.

- Central nervous system and blood cancers were more generously supported than their burden would warrant.
- Screening accounts for 8% of breast cancer papers, 1.7% of lung, 0.59% of oesophageal, and 0.33% of pancreatic research papers.
- An analysis of research domains indicated a paucity of research on radiotherapy (5%), palliative care (1.2%), and quality of life (0.5%).
- The European research portfolio needs to include more activity in surgery and radiotherapy, given their significant role in successful cancer treatment and control.
- There appears to be substantial support for two basic research domains, namely genetics and epidemiology. This focus may reflect the amount of publicity given to these domains in media stories.
- There is a particular need to encourage charitable and philanthropic funding in Eastern Europe, where cancer research support comes almost entirely from the central government.

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## Metawars: Meta-analyses were supposed to end scientific debates. Often, they only cause more controversy

*Science* recently published five papers on metaresearch, a scientific field of its own: “Research on research”, “Journals under the microscope”, “The metawars”, “A recipe for rigor”, and “Toward a more scientific science”.

Editors have created a new field called “journalology”. Metaresearchers have simple messages: Research practices should be questioned more, and if we understood better what we are doing, we might be able to do it better.

The metawars paper explores meta-analyses, as too many have conflicting results. In a meta-analysis, researchers collect all the evidence about a scientific question, weigh it impartially, and declare a “winner”.<sup>1</sup> There were about 11,000 new meta-analyses published in 2017, one-third of them by Chinese authors. This is a marked increase compared with

the fewer than 1000 published in 2000.

A good meta-analysis starts with clear criteria for study inclusion and exclusion. Scientists have to make several decisions and judgment calls that influence the outcome of a meta-analysis, mindful that anyone who wants to manipulate data has endless opportunities. Meta-analyses are popular because they can be done with little or no money, are publishable in high-impact journals, and, in turn, are often cited. Meta-analyses with conflicting conclusions become frequent, for example, in fields such as antidepressants, antiviral therapy for hepatitis C, flu treatments, associations between violence and games, and placebo effects.

Funding is a potential source of bias, but not the only one. Even if Cochrane meta-analyses are more rigorous than non-Cochrane meta-

analyses, that won't always eliminate conflict. Indeed, we recently observed a public dispute among Cochrane directors after the publication of a systematic review on HPV vaccine.<sup>2</sup> Resolving such conflicts is nearly impossible. Ideally, the future will see more transparency in opening up the data to allow colleagues to redo the meta-analysis... hoping that they will have no influence on the results.

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## Is cardiology research leading the way for achieving data sharing, compared to other medical specialties?



Data sharing in medicine lags behind that found in other scientific disciplines. The sharing of de-identified patient-level research data presents immense opportunities to all stakeholders involved in research. The cardiology team from the Yale School of Medicine described the efforts promoted by government, universities, sponsors, and industry players:

- Initiatives for data sharing and reporting of results come from several organisations: FDA (Food and Drug Administration), NIH (National Institutes of Health) and major funders (Bill & Melinda Gates Foundation, for example), PCORI (Patient-Centered Outcomes Research Institute), ICMJE (International Committee of Medical Journal

Editors), PRMA (Pharmaceutical Research and Manufacturers of America, and EFPIA (European Federation of Pharmaceutical Industries and Associations).

- Data-sharing platforms are numerous: government created platforms (NIH), industry-supported platforms such as Clinical Study Data Request, University and non-profit-based platforms such as the YODA Project.
- Many examples of data sharing experiences are described in this paper (SPRINT with the NEJM initiatives).
- The future of open data in cardiology will bring new incentives with researchers capitalising on the productivity of others

rather than creating original data. A “data authorship” system should be created. The sharing of clinical data by patients with researchers holds great potential, for example the NIH’s Sync for Science (S4S) programme.

- The revolution in data sharing that has transformed domains ranging from physics to genetics is just beginning for clinical medicine. Resolving the cost issue will be central to achieving a culture of sharing.

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## Analysis of two clinical trials registers – clinicaltrials.gov and EU Clinical Trials Register

Two different research teams from the UK analysed the reporting of results of clinical trials, with different objectives and methods.

### **US register: Results of industry-funded trials are more likely to be disclosed than those from other funders**

All 45,620 clinical trials evaluating small molecules therapeutics, biological drugs, adjuvants, and vaccines completed after January 2006 and before July 2015 were included.<sup>1</sup> Among 27,835 completed efficacy trials (phase II-IV), 15,084 (54.2%) had disclosed their findings publicly. Industry was more likely than non-profit trial funders to disseminate trial results (59.3% versus 45.3%), and large drug companies had higher disclosure rates than small ones (66.7% versus 45.2%). Trials funded by the National Institutes of Health (NIH) were disseminated more often than those of other nonprofit institutions (60.0% versus 40.6%). Results of studies funded by large drug companies and

NIH were more likely to appear on clinicaltrials.gov than those from non-profit funders, which were published mainly as journal articles. Trials reporting the use of randomisation were more likely than non-randomised studies to be published in a journal article (34.9% versus 18.2%), and journal publication rates varied across disease areas, ranging from 42% for autoimmune diseases to 20% for oncology.

### **EU register: Compliance with the European Commission requirement for all trials to post results on the EUCTR within 12 months has been poor**

The objective of this retrospective cohort study<sup>2</sup> was to ascertain compliance rates with the European Commission's requirement that all trials on the EU Clinical Trials Register (EUCTR) post results to the registry within 12 months of completion (final compliance date December 21, 2016); 7,274 of 11,531 trials listed as completed on EUCTR and where results could be established as due were included. Of 7,274 trials, 49.5% (95% confidence interval 48.4% to 50.7%) reported results. Trials with a commercial sponsor were substantially more likely to post results than those with a noncommercial sponsor (68.1% versus 11.0%, adjusted odds ratio 23.2, 95% confidence interval 19.2 to 28.2); as were trials by a sponsor who conducted a large number of trials (77.9% versus 18.4%, adjusted odds ratio 18.4, 15.3 to 22.1). More recent trials were more likely to report results (per year odds ratio 1.05, 95% confidence interval 1.03 to 1.07). Extensive evidence was found of errors, omissions, and contradictory entries in EUCTR data that prevented ascertainment of compliance for some trials.

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# In the Bookstores

## Strategic Scientific and Medical Writing: The Road to Success

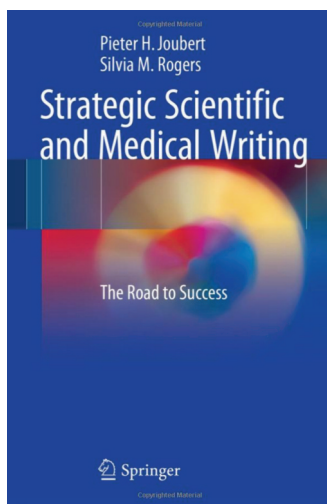
By **Pieter H. Joubert**  
and **Silvia M. Rogers**

Springer, 2015

ISBN 978-3-662-48315-2

(softcover)

GBP 54.99



In *Strategic Scientific and Medical Writing: The Road to Success*, Pieter Joubert and Silvia Rogers describe how to identify the target audience, construct key messages, and recognise the

desired outcome of your document to make your writing more successful. This book is divided into 15 chapters, with the first six chapters providing general advice to medical writers on topics ranging from contacting regulatory authorities to scientific misconduct. The latter chapters focus on specific document types which are commonly authored by medical writers, including investigator's brochures (IBs), the common technical document (CTD), clinical study reports (CSRs), and protocols. This book is aimed at a range of professions and roles within the medical and academic fields.

Chapter 1 introduces the reader to the importance of understanding your target audience: anticipating their level of understanding, considering what the desired outcome of the document is (e.g. acceptance of a publication or approval of a CTD for marketing by a regulatory agency), and recognising the need to familiarise yourself with the relevant regulatory guidelines. The authors introduce a number of different documents that are discussed in later chapters.

Chapter 2 discusses the importance of early contact with regulatory authorities to help speed up the drug development process. Discussing manufacturing formulation and new drug candidate testing early on can help prevent delays downstream. For example, in the US, pre-IND (Investigational New Drug) meetings have seen clinical development time shorten by 3 years or more. Early communication can also lead to tailor-made review and approval procedures such as Fast Track and Breakthrough Therapy (for drugs used to treat serious conditions with unmet

needs), Priority Review (for drugs expected to provide significant advancement in medical care), and Accelerated Approval (for drugs used to treat serious conditions where less effective treatments are available). In these situations the approval is based on intermediate clinical endpoints followed by additional trials performed after approval to confirm the benefit.

Chapter 3 looks at written communication in

academic settings, including scientific papers, master's and doctoral theses, laboratory reports, research proposals, and grant applications. This chapter provides suggested structures for the reports and advice on how to communicate the content effectively. For those working in an academic setting, this chapter may be of particular interest. Chapters 4 and 5 look at language issues for both native and non-native English speakers, such as avoiding the use of colloquial terms and jargon, choice of tense, active and passive writing, essential and non-essential clauses, and the need for experienced translators. Chapter 6 discusses scientific misconduct and Chapters 7 and 8 discuss key statistical concepts and tables and graphs, respectively.

By far the most informative chapters for medical writers are in the latter part of this book. Chapter 9 introduces the reader to the International Council for Harmonisation (ICH) guidelines that provide the structure for documents submitted when applying for approval of new medicines. ICH guidelines cover four categories: quality, efficacy, safety, and multidisciplinary. Application of these guidelines should result in consistency between documents and a more positive outcome (e.g. a high-quality, clear description of the study in a CSR, approval of a CTD by a regulatory authority, or acceptance of a manuscript by a journal). However, the authors highlight the fact that the ICH guidelines are there to guide and that they may not cover all situations; in some cases, deviations from the guidelines may be required. Although this chapter provides a nice overview of the

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guidelines, no one guideline is discussed in detail and the reader is required to consult the ICH website if further information is required.

In Chapter 10, the authors discuss the importance of updating the IB. The IB is a living compilation of an investigational product's nonclinical and clinical data. It not only provides the investigator with necessary background information such as the dosing rationale, but also provides the reference safety information for a product in development. The IB is an important document during the regulatory approval of a trial and submission to ethics committees. This chapter highlights the importance of keeping the IB succinct and clear by the removal of unnecessary nonclinical data when advancements are made in the clinical development. This makes the document easier to read and facilitates the transfer of key messages, thereby safeguarding the safety of subjects, and allows clinicians to form unbiased and independent benefit-risk decisions. Notable parts of this chapter include useful links to the ICH guidelines and a summary of content to be included in an IB that gives the writer a structure to follow. The different emphasis that the EMA, US FDA, and ICH have on the IB is also discussed, with the ICH and EMA viewing the IB as a Good Clinical Practice document to inform the investigator and the FDA seeing the IB as part of the IND application with a stronger emphasis on safety. This chapter also discusses the key messages of the IB and reiterates the common theme of the book, which is to know your audience and adapt your writing accordingly.

Chapter 11 describes the initiation of clinical programmes. Broadly speaking, European countries require a clinical trial application (CTA) and the US requires an IND application in addition to the IB. Chapter 11 goes further to describe the various components of the IND application and CTA. The authors highlight that information in an application should include (but not be limited to) the current knowledge of the drug, rationale

for the indication, and medical need for the drug; show an acceptable benefit-risk ratio; have sufficient nonclinical data to identify a safe starting dose and a maximum dose; and list clearly the safety parameters to be monitored. This chapter presents summaries of the CTA and IND application succinctly in tabular format and provides useful web links for further reading. Although the title of this chapter includes the Investigational Medicinal Product Dossier (IMPD), I feel this chapter would benefit from more discussion of the IMPD, as its content is relatively unfamiliar when compared to more commonly authored medical writing documents such as CSRs and IBs. As in Chapter 9, readers may need to use the web links to find out more, but the chapter does provide a useful basis to work from.

Chapter 12 discusses the key components of the CTD including information on efficacy, safety, and quality. The CTD provides a format for applications to register new drugs. The chapter describes how it consists of five modules split into three main components: Module 1 – Administrative Information; Module 2 – Summaries of the Quality from Nonclinical and

Clinical Data; and Modules 3, 4, and 5, which include the nonclinical and clinical data referenced in Module 2. This chapter focuses primarily on Modules 2.4 and 2.5 (nonclinical and clinical overviews) and provides some very useful information on length, content, structure, emphasis, common mistakes, and relevant links to guidance. The authors also highlight the ultimate purpose, which is to obtain marketing approval.

Chapter 13 looks at study protocols, with a focus on the rationale, objectives, study populations, and study design. The second half of this chapter provides a brief summary of CSRs and abbreviated CSRs, emphasising that regulatory authorities are the audience and that the key messages must be clearly reported. Although much of the information in this chapter may be known to experienced medical writers, I think it provides a useful refresher, with tips on planning, template guidance, and links to guidance on ethics, informed consent, and abbreviated reports.

The book concludes with Chapters 14 and 15, which look at scientific papers and publication strategy, respectively. These chapters complement

each other and provide useful information about planning a paper, selecting the right journal, and the timing of submission.

Overall, this book provides insight into the themes of knowing the purpose of the document you are writing, knowing your audience, and adapting to their requirements. I feel this book covers some lesser known medical writing documents as well as providing useful advice on more commonly encountered documents such as CSRs and protocols. Each chapter complements the others and the reader gets a good understanding of how the various documents interlink. I would recommend this book as a good basis to learn from; however, due to the nature of the guidelines and the documents described, a comprehensive discussion of each falls beyond the scope of this book and readers should be prepared to follow the suggested links to discover more detail.

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# Good Writing Practice

## Syntactic structure

Circumlocution: Nominalisation + perfunctory verb



### Introduction

Nominalisation is the transformation of a precise verb into another sentence constituent, usually a noun (nominalisation), sometimes an adjective (adjectivalisation). This syntactic transformation elicits the grammatical necessity to add an imprecise (i.e., perfunctory) verb (see Box).

Collectively the nominalised and the perfunctory verb add to other types of syntactic circumlocution such as dependent clauses and absolute phrases. It could be argued that usage of a perfunctory verb is a semantic distraction, characterised by imprecision and non-professional tone. However, the syntactic taxonomy provides insight into the underlying cause of the distraction and, in turn, its revision.

On the positive side, nominalisation results from thematic focus; that is, placement into the subject position the conceptual topic of a

sentence rather than agents responsible for the action. The first sentence in this article is an example: *Nominalisation is the transformation of a precise verb into another sentence constituent.* Such nominalisation is often accompanied by the verb *to be*. Another verb characteristic is usage of the passive voice as in *The taxonomy as non-professional tone is justified by the lack of verb precision.* Overall, nominalisation contributes to an academic formal descriptive style. However, on the negative side, nominalisation results in burying a precise action verb and replacing it with an actionless linking verb or unnecessary perfunctory verb.

The examples in this article are organised

However, on the negative side, nominalisation results in burying a precise action verb and replacing it with an actionless linking verb or unnecessary perfunctory verb.

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according to sections of a journal article (Experimental and Contextual), their conceptual components, and the sentence constituent into which the precise verb is nominalised. In addition, an example of verb adjectivalisation is presented.

### Experimental sections

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

**Example: Nominalised sentence subject**

The *isolation* of the tertiary component was *accomplished* by the following:

**Revision (de-nominalisation)**

The tertiary component was *isolated* by the following:

#### Notes

The most typical nominalisation involves a precise verb that is transformed into a noun subject. In the example, the specific verb *isolated* is nominalised into the sentence subject *isolation*,

grammatically necessitating the usage of the perfunctory verb *accomplished*. In addition to imprecision, over-usage of perfunctory verbs results in synonymous verbs (synonymy) each with slightly different connotations, especially in the Materials and Methods section where the succession of methods necessitates repetition of action verbs.

In the revision, de-nominalisation results in (1) precision: the perfunctory verb *accomplished* is replaced by *isolated* and (2) concision: the perfunctory verb

and the preposition *of* are deleted, so that the revision consists of three fewer words.

However, when the nominalised subject is thematically focused on the conventional usage in a discipline, its usage along with a perfunctory verb (e.g. *perform*) may be preferred. For example, *In situ hybridisation was performed*, rather than *cells were in situ hybridised*.

## Part 2 – Results section: Data-based observation

### Example: Nominalised direct object

Compound A *caused* a significant *inhibition* of leukotriene synthesis.

### Revision (de-nominalisation)

Compound A significantly *inhibited* leukotriene synthesis.

### Notes

*Inhibited* is clear and direct language whereas *caused a significant inhibition* is indirect. In the example, the potential precise verb *inhibited* is nominalised into *inhibition* grammatically necessitating the usage of the perfunctory verb *caused*. *Caused* may not at first seem perfunctory, but it is compared to *inhibited*. In addition, the three-word difference between the example and revision characterises the example as a circumlocution.

## Contextual sections

### Part 1 – Introduction section: Research hypothesis

#### Example: Nominalised gerund object in a prepositional phrase

The erythrocyte *may function* by *supplying* developing tissues with linolenic acid.

### Revision (de-nominalisation)

The erythrocyte may *supply* developing tissues with linolenic acid.

### Notes

In the example, the potential precise verb *supply* occurs as the gerund object of the preposition *by*, thereby necessitating usage of the perfunctory verb *function*. De-nominalisation (*by supplying* → *supply*) eliminates the perfunctory verb *function* and the preposition *by*, also reducing the word count from 11 to 9.

### Part 2 – Discussion section: Limitation

#### Example: Adjectivalised past participle

Baseline counts *could contribute to altered* haematocrit.

### Revision (de-adjectivalisation)

Baseline counts could *alter* haematocrit.

### Notes

Transformation of a verb into an adjective (or adjectival) necessitates the use of a perfunctory verb. In the example, the transformation of the verb *alter* into the adjectival participle *altered* necessitates the addition of the perfunctory (phrasal) verb *contribute to*, so that the sentence is grammatical. A phrasal verb consists of a verb and a preposition-like word, such as *contribute to*.

Another characteristic of a phrasal verb is that the preposition-like word *to* cannot be shifted to a position other than contiguous to the verb. In the Revision, de-adjectivalisation results in the deletion of *contribute to*.

## Summary

Nominalisation + perfunctory verb, particularly subject and direct object positions, is a common distraction in the experimental sections (Materials and Methods, Results) of journal articles. Such nominalisation is less obvious in the conceptual sections (Introduction, Discussion). Although the circumlocution is a dissonance, the imprecision of a perfunctory verb is a nonprofessional tone. For all of the examples in this article, de-nominalisation (or de-adjectivalisation) eliminates the perfunctory verb, reinforcing the principle that the nomenclature of a syntactic distraction (e.g. nominalisation + perfunctory verb circumlocution) is a cue to its revision.

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## Common perfunctory verbs

Accomplished <sup>1</sup>	Given
Achieved	Implemented
Attained	Made
Conducted	Obtained
(Contribute to) <sup>2</sup>	Occurred
Demonstrated	Performed
Done	Produced
Effected	Realised
Employed	(Resulted in) <sup>2</sup>
Executed	Showed
Exhibited	Taken
Experienced	Used

- 1 The past participle instead of the verb stem (e.g. *accomplish*) is listed because the participle is the most frequent form in the passive voice (e.g. *something was accomplished*). Only transitive verbs can be expressed in the passive voice, whereas intransitive verbs cannot (e.g. you cannot say "*something was functioned*").
- 2 Phrasal verb (see Adjectivalised Past Participle).



# Getting Your Foot in the Door

## Editorial

Before one can get one's foot in the door, one needs to be aware that there is actually a doorway. This is the mission of the EMWA Ambassador's Programme – to inform the world about medical writing as a career path. In other words, we set up signs that lead to the door.

In this edition of GYFD, Abe Shevack, who pioneered this initiative, provides an update on the latest ambassador activities.

In September, I was on a 2-week business trip in the Asia-Pacific region. I was able to take a short weekend trip to the Philippines to visit my family and be an EMWA Ambassador at a careers event at my alma mater. I would like to thank Michalyn and Jude, two Biology students who volunteered to write about the event.

Raquel

## Ambassador's Programme update

The EMWA Ambassador's Programme is going along at a steady pace as we are spreading the word about medical writing and EMWA at universities and career events across Europe.

On June 27, EMWA fellow John Carpenter attended a medcomms career event at the University of Westminster organised by Network-Pharma Ltd with over 80 post-docs and PhD students and representatives from 15 agencies in attendance. John also attended another career event organised by the same organisers on September 13 at the University of Manchester. At this event 14 agencies were represented. There were pre-presentations about careers in medcomms given by representatives of these agencies. John networked and answered questions from participants and provided them with information on EMWA.

On July 5, EMWA past President Abe Shevack, and Raquel Billiones held a day-long workshop on clinical trial protocols, CSRs, and clinical trial transparency at the BioM biotechnology network event in Munich. There were over 20 enthusiastic participants from biotech and clinical development in attendance. The feedback was very positive and we may be cooperating with BioM in the future.

Also on Sept. 24, Raquel Billiones was in the Philippines and represented EMWA at a careers talk at her alma mater. A write up of the event is provided below.

Finally, on October 25, Franziska Abreu, EMWA Sponsorship Officer, gave a well-received presentation about careers in medical writing and the benefits of joining EMWA at an event organised by doctoral candidates and post-

doctoral fellows at the Max Planck Institute in Marburg, Germany.

The Ambassador's group and other interested participants held a lunch table meeting at the Warsaw conference on November 8 to discuss the current status of the programme and ideas on how to proceed in the future.

The Ambassador's Programme now has a page on the EMWA site listing news and past and upcoming events (see <https://www.emwa.org/about-us/ambassadors-programme/>).

In order to keep the momentum going, we are always looking for experienced presenters who have previously volunteered as either workshop leaders or served on one of EMWA's committees.

If you are interested in serving as an Ambassador or if you have heard about any upcoming career events that EMWA might attend, please contact me or the EMWA Head Office ([info@emwa.org](mailto:info@emwa.org)).

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## Career talk: What does the future hold after a bachelor's degree in biology?

**September 24, 2018** – Organised by the University of the Philippines Ecological Society (UPECS), a 3-hour Career Talk for Biology Students was conducted at the Arts and Sciences Hall, an event aimed to embolden biology students, seniors and freshmen alike, to think about their future (Figure 1).

Nuela Pauline Tabat, UPECS Secretary, welcomed approximately 70 students and guests to the event. She also introduced the speakers for that afternoon.

The seminar was divided into two sessions. Co-founder of Cebu Innovative Network (CIN) – a techno-hub for creative communities, Mr Paulino Llido, graced the first session. He gave an enlightening talk about biotechnology as a career for graduating students.

Dr Raquel Billiones, representing the European Medical Writers Association, had the floor during the second session in her talk "Loves Science, Likes to Write: A Career in Medical Writing." Raquel is currently heading the Medical & Regulatory Writing Group of Clinipace Clinical Research, a global mid-sized CRO.

She began with an introduction to the different types of medical documentations that medical writers cover. Medical writing, she added, is a promising career

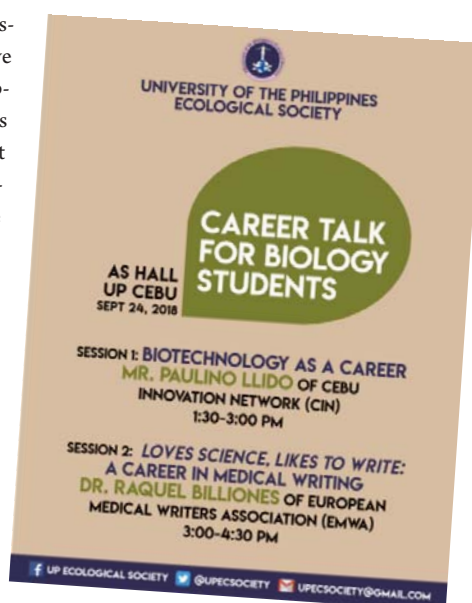


Figure 1. Event programme



gets market approval and makes a difference in people's lives.

It has been the norm that the graduates with bachelor's degrees in biology would flock to medical schools to become physicians. Some who opt out of studying medicine would become researchers or educators. That afternoon, the students were enlightened with a new set of possibilities that they can stray from the paved path of medicine and academia if they wish to. The career talk seminar established that there are other careers that can be taken into consideration when thinking about the future. It is this realization that the students brought home and will surely ponder on (see Figure 2 for the event group photo).

The career talk seminar established that there are other careers that can be taken into consideration when thinking about the future.

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as writers can work in various settings such as pharmaceutical and biotechnology companies, government agencies, research institutions, and hospitals. The writers can also be self-employed and/or home-based.

Raquel then addressed the gnawing hesitation of the students towards the career by saying that we need not be medical doctors to enter this field. She added that a background in a field of science and a good command of the English language are key to success in medical writing. Since Filipinos are proficient in English, medical writing, according to her, is well-suited for the science students who attended the discussion.

In the open forum, interested students addressed their questions to Raquel. When asked about coping with writer's block, she responded, "It is very normal to have writer's block. Just take a break. When I experience writer's block, I jog," which amused the audience. She ended the talk by showing a YouTube video that gave the audience a glimpse of the fulfillment that comes when a treatment that a medical writer supports



Figure 2. Group photo of participants in career talk seminar

# My First Medical Writing



## Editorial

After the debut of the first edition of this section, I was honoured to be contacted by many aspiring medical writers eager to contribute and to showcase their writing skills. Among them, Matias Rey-Carrizo did an

amazing job in translating a complex and controversial topic into an enjoyable read. Matias has a PhD in medicinal chemistry and an extensive experience in scientific publications. After his last postdoctoral stay in Tokyo, he embarked on a medical writing

journey as a freelancer at BCN Medical Writing. We hope you'll enjoy reading this article as much as we enjoyed creating it. If you're trying to get your foot in the door or know someone who is, don't hesitate and contact us!

## Cannabis's comeback: New lessons from an old plant

In June 2018, the US FDA gave the green light to an oral solution of cannabidiol, the first drug containing a substance purified from cannabis.<sup>1</sup> To appreciate the magnitude of this announcement, let's recall the history of medicinal cannabis.

The term cannabis includes all plants of the genus *Cannabis*. Cannabis use has been documented since 4000 BC.<sup>2</sup> The plants have been cultivated for its fibres – so-called hemp – or for therapeutic purposes.<sup>3</sup> Cannabis's best studied medicinal properties include antiemetic, analgesic, anticonvulsant, and antimigraine effects.<sup>3,4</sup>

During the late nineteenth and early twentieth centuries, cannabis was included in Western pharmacopoeias, such as the British and American pharmacopoeias,<sup>3</sup> and several pharmaceutical companies (e.g. Merck, Bristol-Meyers Squibb, and Eli Lilly) were marketing cannabis extracts or tinctures.<sup>5</sup> However, cannabis was excluded from the American pharmacopoeia in 1941 because of the highly variable effects

from different samples of the plant and the development of more effective medications (e.g. vaccines, aspirin, and barbiturates).<sup>5</sup> Most European countries followed the US lead in 1971.<sup>4</sup> In the 1960s, while the recreational use of the drug was soaring, the chemical structure of the main psychoactive ingredient,  $\Delta^9$ -tetrahydrocannabinol (THC), was revealed.<sup>6</sup> The finding sparked a new interest in the therapeutic effects of the plant constituents and a spike in related publications. However, this increase was small compared to the one that occurred in 1988 with the discovery of the endocannabinoid system, composed of specific receptors in the nervous system sensitive to cannabis components<sup>7,8</sup> and a naturally occurring agonist, anandamide.<sup>9</sup>

To date, more than 460 compounds have been identified in cannabis, although only a handful are considered of therapeutic interest.<sup>4</sup> Until recently, the FDA had approved only two drugs derived from cannabis. The first, dronabinol, a synthetic form of THC, was licensed in

1985 as an appetite stimulant for people with AIDS and as an antiemetic for patients receiving chemotherapy.<sup>10</sup> The second, nabilone, a synthetic derivative of THC, was also approved in 1985 but was not marketed until 2006 and is indicated for chemotherapy-induced nausea and vomiting.<sup>11</sup> Further studies have revealed a potential for nabilone to treat chronic pain, for example, in multiple sclerosis.<sup>12</sup> Also noteworthy is nabiximols, an extract of cannabis containing THC and cannabidiol available in the UK and other Western countries, which is used for treating symptoms of multiple sclerosis, although this drug has not yet been approved in the US.<sup>13</sup>

Given the controversial matter of smoked medicinal cannabis, the trend has been to get away from natural preparations of unknown content and potency and, instead, develop drugs from isolated components with verifiable composition, stability, dosage, and pharmacology. For instance, when cannabidiol interacts with THC they produce variable outcomes.

## SECTION EDITOR



Evguenia Alechine

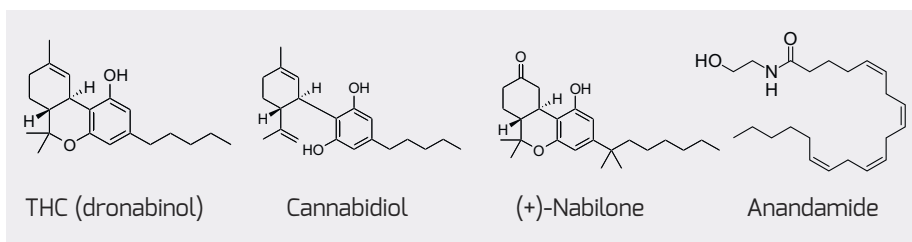
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Figure 1. Three species of the genus *Cannabis*.

From left to right: *Cannabis sativa*. Photograph by Thayne Tuason, distributed under CC BY-SA 4.0 licence. *Cannabis indica*. Photograph by Aleksander sowa (copyright free). *Cannabis ruderalis*. Photograph by Le.Loup. Gris, distributed under CC BY-SA 3.0 licence.





**Figure 2.** Chemical structures of  $\Delta^9$ -tetrahydrocannabinol (THC) or dronabinol, cannabidiol, nabilone (a synthetic derivative of THC), and anandamide

Moreover, smoking cannabis or whole-plant extracts carries a risk of pulmonary damage or dependence, among other adverse effects.<sup>14</sup> Although there is evidence of the benefits of medicinal cannabis for chronic pain and for the palliative care of terminally ill patients, smoked cannabis is generally discouraged because of safety concerns, variable effects (preparation and interpersonal variabilities), and lack of quality control.<sup>14,15,16</sup>

In the US, until recently, the only approved drugs derived from cannabis were chemically synthesised. As mentioned above, this changed in June 2018 with the approval of cannabidiol, the main non-psychotropic constituent in *Cannabis sativa*.<sup>1</sup> Cannabidiol is structurally related to THC and interacts with the endocannabinoid system.<sup>17</sup> Clinical trials showed that cannabidiol reduces seizures in Dravet and Gastaut syndromes, two rare forms of epilepsy affecting children and infants.<sup>18,19</sup> As a result, cannabidiol was the first treatment approved for the Dravet syndrome and as a complementary treatment for the Lennox-Gastaut syndrome.

As with smoked medicinal cannabis, the usage of cannabidiol oil is also controversial. Its products have variable content of the active ingredient and are not approved by any regulatory agency. However, these preparations have been used for epilepsy, cannabis dependence, epidermolysis bullosa (a skin disorder), anxiety and insomnia, among other conditions.<sup>20,21,22,23</sup>

Finally, thanks to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), approval of cannabinoids in one country may lead to more widespread approval. Thus, extraction or synthesis of molecules from this mystical plant may lead to a new approach to medicinal cannabis.

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# Out on Our Own

## Editorial

### Welcome readers,

This issue of *Out on Our Own* is jam-packed with essential tips for any new freelancers or those tempted to become freelancers. Taking that step to becoming a freelancer isn't only about finding clients, there's so much more involved that perhaps isn't obvious at first.

Every client or contact will be a learning experience, no matter how long you've been in the business. Projects are rarely identical. Thus, contracts, document content, client relationships, etc. will differ with each one you deal with. And then comes the practicalities of being

self-employed in a particular country, paying taxes, dealing with client payments etc. With our laptops and phones securely by our sides nowadays, can a freelancer ever switch off?

In this issue, three experienced freelancers have taken the time to summarise their basic or essential rules of being a freelancer. First, Katharina Kolbe gives her five basic rules that she still applies to her clients after 5 years of being a freelancer. Second, Silvia Paz Ruiz offers some secure backup ideas and talks about how important it is to have healthy habits and look after yourself. After all, if you're ill you'll be unable to meet that deadline! In the third and

final article, Sarah Smith offers a very different approach to freelancing, from her yacht, which is also her family home, office, and means of transportation on her 11-year quest around the world. Warning, you may be tempted to pack up and sail away with your laptop!

Every freelancer will have a different journey, and experience different clients. I, and the three freelancers here, hope that their experiences and knowledge may be just the friendly advice you've been looking for.

Happy freelancing!

**Laura A. Kehoe**

## “Dealing” with clients

Over already five years of freelancing I signed contracts of very different kinds. Every single one of them has been an individual contract that my client and I dealt with. I haven't had any problems with settling my bills in the last two years, except for one special case. He was satisfied with my work and already asked me to work on a new project. I waited for three months, sent him payment reminders, called him, and even threatened to give his case to my lawyer (which I actually didn't). We finally agreed on a partial payment, which was of course not satisfying for me, but at the time I just did not want to spend money on a lawyer. And by the way, it seems important to me to solve any problem bilaterally, without consulting lawyers. I am always a very open-minded person, which my clients appreciate. Of course, every single one of us will be responsible for own mistakes now and then, but maybe my “basic rules” will help some of you to avoid unnecessary stress, discomfort, and unpaid invoices.

### 1. Fixed budget or hourly rate?

This question is almost as hard to answer as that of the chicken and the egg.

In case you go for a fixed budget, make sure to write down an emergency exit to get additional work paid. You will need to write clearly to your client as soon as you recognise that you will definitely run over the budget. State the reasons to your client, and why the project requires extra

time and money. In all cases: do it in advance!

Working on an hourly rate is very transparent for your client. But there might be a certain risk that you will be asked why a specific project milestone took you so long.

Both approaches have its own advantages and disadvantages. I personally offer a mixture: usually, my client will get an estimation of the time I need for different project steps with my hourly rate. From this, I can estimate the needed overall budget, which is usually the price tag on my invoices. This depends on good predictability of the project.

### 2. Timelines and project management

Discuss the timelines with your client and always try to get as much time as possible – just in case. It is always better to deliver your work earlier than too late (“better to be safe than sorry”). Make clear that delays on the part of the client will lead to adjustments of your timelines as well. You do not only have one single client, nor will you be waiting for his feedback for weeks, right?

### 3. Payment terms

There are many different models on how to split the budget for smaller invoices. Some other EMWA freelancers told me that they demand a payment in advance of completing their projects. I think this is a good idea and I do this with new clients. You can agree on an advance payment

of 20% to 50% as an integral part of your contract. My payment schedule relates to the project steps, and my client will get several invoices for one project, usually as soon as one project step is delivered. Of course, my invoices contain a payment target. In some cases, clients will not accept other payment targets than their own ones. This is something you cannot avoid, but do keep track of payment delays and send friendly reminders to your clients as soon as possible.

### 4. Still unsure about your client?

If your gut is telling you that there might be something wrong with your (potential) client, check the company on the internet for reviews or experiences of former employees or maybe ask other EMWA freelancers for their experiences. A face to face meeting that gives you the opportunity to discuss the projects' scope and honoraria with your potential client can also be a good idea. Make sure at least your travel expenses are covered.

### 5. Some further safeguards

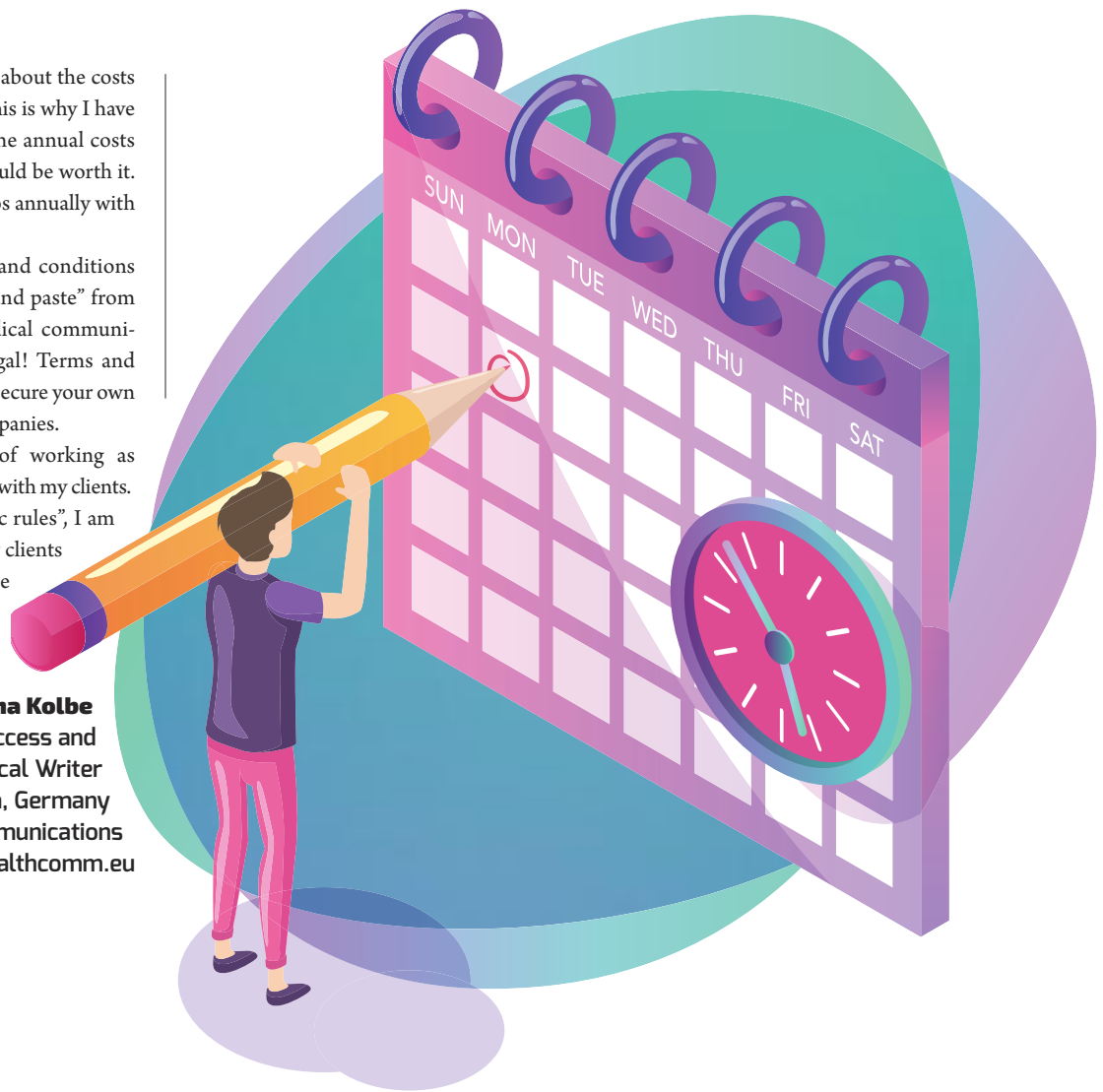
Think about liability insurance or even a limited liability company. The costs for this differ between different countries and can be extremely high. Talk to your tax consultant or discuss it at home with your family. To avoid any indemnity issues, another freelancer recommended never signing any indemnity clauses in contracts. Being

a freelancer in Germany, I know about the costs of a limited liability company. This is why I have a business liability insurance. The annual costs can also be rather high, but it could be worth it. I found one for about 1,000 euros annually with a high sum insured.

Discuss and develop terms and conditions with a lawyer. Never do “copy and paste” from another medical writer or medical communications freelancer – this is illegal! Terms and conditions can be a good way to secure your own work against (much) bigger companies.

Overall in these 5 years of working as freelancer, I have been very lucky with my clients. Now considering my own “basic rules”, I am able to better concentrate on my clients and my work, which actually is the key issue.

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## Taking care of yourself (and your freelance business)

In setting up a freelance business there are three aspects that I found crucially important, but frequently forgotten. The three of them relate to planning ahead and for the long-term: contingency planning, disability insurance and healthy habits.

### 1. Contingency planning

Contingency planning is about having a series of actions in place to prepare yourself to respond well to an emergency, an unexpected circumstance that may have catastrophic consequences and a deleterious impact on your business. Having a contingency plan is like having a “Plan B” to be able to timely undertake “disaster-relief” operations in an effective manner.

Backing up files is a critical component of a contingency plan in freelancing. It ensures that important documents or data can be recovered in the event of computer failure, computer loss, or other equivalent adversity (particularly if such event occurs just hours before a deadline!).

The traditional method of backing up is to have an external hard-drive on the working desk. It may be the preferred option for most freelancers, and it is sometimes perceived as more secure than using “the cloud” to store data. However, any physical building (e.g. home, coworking space, or office) can fall victim to theft, fire, or flood, thus endangering the backup solution. A protected solution using an encrypted online backup service to store important files at a remote location is probably the most advisable contingency alternative. Furthermore, it is preferable to use a combination of two or more reliable backup solutions for contingencies.

Possible backup resources are endless, but the most well-known ones include Dropbox, One Drive, and Google Drive, which are all based on online file syncing. Drive File Stream, NetVault Backup, or Sugarsync allow for documents to be either manually or automatically backed up on the providers’ servers according to your preferred backup schedule (e.g. hourly, daily, weekly).

Once backed up, updated files can be recovered remotely from any computer that is connected to the internet by using your log-in credentials.

It is important to remember that according to the EU General Data Protection Regulation, approved in 2016 with enforcement beginning in May 2018, any time any sensitive data (e.g. client emails, bank details, addresses) as well as any confidential documents are stored in the cloud, files should be password-protected or encrypted. It is therefore important to be clear about how your cloud provider is storing and processing data (you may wish to visit <https://eugdpr.org/the-regulation/> for further details).

Along with backing up files, it is also good practice to have alternative computers to work on in case the main one fails; to check out alternative venues for working in case you cannot stay at your usual place, making sure that free wi-fi access is available, and that sufficiently quiet spaces exist for making phone calls or for keeping confidential conversations, if needed. It is also

advisable to be able to delegate any of the work to other freelancers in case of illness or any other unexpected situation. Having a reciprocal cover arrangement with someone you trust and whose work you like may be a good option.

## 2. Disability insurance

As a freelancer, you can lose your income if you are unable to earn a living. Disability insurance is an insurance policy that protects you from loss of income if you cannot work due to illness, injury, or accident for a long period of time. Having disability insurance means you will get income replacement cheques while you are unable to work. It is highly advisable to secure disability insurance that will eventually relieve your anxiety and uncertainty in such circumstance.

Disability insurance policies come with many different features that can add up in terms of cost. They differ based on what is covered, payouts, length of time, and other factors; they define what constitutes a disability, including mental and physical conditions, and do not cover your entire salary. Therefore, it is important to consider the short- and long-term financial scenarios you might face in the event of a disability when deciding what your policy design should look like. You will need to determine the percentage of your current monthly income for which you would like to apply.

It is also worth considering that each country

has disability insurance programmes for self-employed professionals, although a great deal of variation regarding rules and regulations exists across regions. It is important to look for and get information about conditions and possible alternatives that are locally available in your place of residence, as well as to talk with representatives from several insurance companies to compare offers and to get an informed sense of options.

## 3. Healthy habits

As a freelancer, long working hours seated at a computer may easily turn into an unhealthy lifestyle with little physical exercise, deficient diet, and little socialisation. All these poor habits are deleterious for your health in general, but also for your brain. Thinking skills and optimal cognitive performance are crucial to keep your freelance work.

Aerobic exercise helps improve the health of the brain tissue by increasing blood flow and by reducing the chances of injury because of high blood pressure and atherosclerosis. It also stimulates the brain to release brain-derived neurotrophic factor, a molecule essential for repairing brain cells and for creating connections between them. Devoting at least 150 minutes per week (20 to 30 minutes per day) to practising moderate-intensity exercise (e.g. brisk walking) may make an important difference to your brain function, and to your overall health.

Eating lots of fruits (including strawberries and blueberries), vegetables (dark, leafy greens such as kale, spinach, and broccoli), and whole grains; getting protein from fish with omega-3 fatty acids (e.g. salmon, mackerel) and legumes; and choosing healthy unsaturated fats (olive oil, canola) over saturated fats (butter) would make the best diet for your brain and body.

It has also been found in research that engaging in mentally stimulating activities creates new brain connections and more backup neuronal circuits that would serve as a cognitive reserve for the future. Socialising is also fundamental for robust emotional support and for achieving higher levels of brain-derived neurotrophic factor. So, freeing up time for taking a new exercise class with a group of friends, a language course with colleagues or trying new recipes for your loved ones will be well paid off.

Ultimately, your health is what will allow you to continue to work and earn a living. You can't afford to put your health in danger; so, take your habits seriously.

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## Extreme freelancing: Writing while travelling

In April 2007, I set sail with my husband and two kids (then aged 7 and 9 years) from our home port of Aberystwyth (UK) on a 43-foot yacht with grand plans “to sail around the world”. I was a freelance medical writer and going to be the main wage earner during our trip. Eleven years on, we haven’t managed to sail around the world but we are still sailing, and I am still working as a freelance medical writer. We have spent time in Northern and Atlantic Europe, the Mediterranean, The Gambia (West Africa) and the Eastern Caribbean island chain (Trinidad and Tobago, Grenada, St Vincent and the Grenadines, Martinique, St Lucia, Dominica, and Sint Maarten). Here are a few thoughts on how we did it plus some of the things that we learned along the way.

### 1. Where will you be travelling and how long do you want to be away?

The time that you intend to be away will affect how you set things up to leave. If you are planning to be away for just a few months, many things can probably be left in place or temporarily stopped and picked up again when you get home. You will need to work through what happens about your house/car/cat/dog/garden/mail/bills/tax return/medication, etc. For us, getting to the point of making the boat our home for an unspecified period meant considerable downsizing and reorganising (e.g. selling the house and cars, rehoming the labradors, and setting up to homeschool).

We had our boat (which is a compact, self-contained apartment) as our means of transport, our accommodation and my mobile office. We planned to keep moving, staying in various places for a few days to a few months, and we intended to be away for ‘a few years’ (whatever that meant because we really weren’t sure at the time!). You will need to consider whether you are going to be moving around or travelling to a particular place (or places) and staying put for a while. It’s probably also a good idea to have a “Plan B” to get home if things don’t work out and you hate it (even if this is just room on your credit card to buy a flight home).

Managing family expectations and commitments may also shape your travelling plans. Do you need to consider ageing parents, kids at school or college, and important family events (planned or otherwise)? Is your Mum

SY Cape



Image courtesy of Sarah Smith

expecting you to throw a party for her 90th birthday in the middle of your trip? Is it practical/affordable to fly back on regular visits or in an emergency if necessary?

### 2. Accountants and clients: key players in our travelling plans

One of the most important phases of planning our trip was to work with our accountant to explore our options, and to put everything in place before leaving. Our accountant is happy to deal with us from a distance and with Her Majesty’s Revenue and Customs, etc., on our behalf. I remain a UK sole trader with a tax liability in the UK (the implication being that I am not liable for tax in another country), but things can be arranged in other ways too. A lot will depend on your own business structure and needs, and how long you intend to be away.

I also discussed our plans with my clients at the time to find out whether they would be happy to continue working with me at a distance. Most were supportive and accommodating, and I have gained new clients along the way. One of my priorities is clear communication about the tasks that I can and can’t take on, project scheduling and timelines when we are actively moving, working across different time zones, and any limitations that I might have with internet access. Home working is much more common now than it was when we left over a decade ago, so most clients are happy to work with freelancers on this basis.

### 3. Practical issues

**Visas:** Foreign holidays and business trips have made us all aware that countries vary in their regulations about whether you need a visa to enter, but it’s not until you travel for longer that you find out that there are often restrictions on how long you can stay and whether you can work. As I was working as a UK-based freelancer, we always entered countries on a pleasure visa rather than a business visa (which was often of limited duration and required sponsorship from a local business). It is worth doing your homework on how different countries organise their visas and work permits so as not to fall foul of these laws by accident.

**Passports:** Many countries insist on there being at least 6 months left on your passport on entry, so passport renewal (if necessary) should be built into your travel plans. We have renewed passports from abroad in the past, but things change so don’t assume that this will be possible when you need to do it. Some airlines will not allow you to fly into a country unless you have a return ticket or flight out to another destination. Once you are in, it is important to be aware of how long you can stay, and not to overstay your allocated time – Immigration Authorities are not to be messed with.

Once you are in, it is important to be aware of how long you can stay, and not to overstay allocated time.

**Banking:** We use online and telephone banking with a UK bank so no different from most personal and business banking arrangements these days. Getting hold of new bank cards when they need replacing can be interesting from abroad, so it is a good idea to have more than one debit/credit card (and keeping one in a separate, safe place so that both can't be stolen if you fall prey to pickpockets). Bank charges for withdrawing foreign currency outside the UK can be expensive, so it is worth investigating debit cards that can be loaded with different currencies (e.g., Caxton) and that don't incur charges.

**Invoicing and payments:** All of my invoicing is done by email, and payment is by BACS – probably like most other freelancers.

**Mail:** We are lucky to have friends who are happy for us to use their address and accept mail for us. They open and scan items that they think we might need to make decisions about, and courier items if appropriate. This can be quite a bit of paper to deal with (even though we opt for “paperless communication”), so it is important that whoever might fulfil this role for you understands what they are letting themselves in for. There are alternative (paid) mail management services available if you don't want to inflict this responsibility on friends or family.

**Telephone and internet access:** My main telephone is a UK mobile number with a monthly contract for calls and mobile data if I choose to use it; obviously this is used on roaming (with attendant costs) when I am outside Europe. I also have a second mobile with a local SIM card for local phone calls and mobile data (which gives me wi-fi for my laptop via the phone's hotspot); we have found this to be the cheapest way of buying data. (In the past, I had a lovely dual-SIM mobile that took both my UK and local SIM cards, but I fell in the sea with that one!) For times when I haven't needed good internet access, we have relied on wi-fi in internet cafés, tourist information offices, cafés, bars, and hotels. Some hotels have business centres that you can use on a pay-as-you-go basis.

**Equipment:** How much equipment do you really need to be able to work on a day-to-day basis? Before we left, I had a home office with a desk, adjustable chair, bookshelves of reference books, a collection of publications that I'd worked on, a filing cabinet, and a printer/scanner in addition to my laptop. While

travelling I manage with a laptop on the table, plus my mobile phone. We don't have room to store much in the way of paperwork or reference books, so I have to keep these to a minimum. We do have a small printer/scanner (which does make life easier), but I could manage without that as it is possible to get printing done at print/stationery shops, internet cafés, and hotels. We are all working towards a paper-free existence and this tends to happen naturally if one loses the ability to print and store paper. I do keep data backups on hard drives, and one day I will set up backing up to the cloud. For me, this is limited by variable internet access.

**Insurance and healthcare:** We took out a family healthcare plan that covered us for major health incidents such as hospitalisation and repatriation if required. As there was quite a large excess on this, we did not make any claims but paid for GP and dental consultations as we needed them. To give a ballpark figure, this usually worked out to about £30 per GP consultation (in Europe and the Caribbean). Some travel insurance policies will include healthcare cover, depending on where you are going and how long for. We didn't take the boat to the USA for a variety of reasons, including the fact that healthcare cover would have been extremely expensive. Our personal belongings are covered on the boat insurance.

#### 4. Making the most of travelling

Having a regular home and work life is streamlined and efficient (trust me – compared with working while travelling – it is). The chances are that working while away from your home environment is going to take much more time to organise (possibly in another language) and execute, so don't plan to work full-time, at least

not until you are sorted. Build in slack to allow time for the unexpected to happen without scrambling your plans, and to minimise the stress that will wreck your trip. There is nothing worse than getting to the hotel that you selected because of its 'free wi-fi in every room' to find that the wi-fi router has died. You won't be the first freelancer to be working to your deadline in McDonald's to get the 30 minutes of full-fat wi-fi that comes with your Big Mac (yes, that is the voice of experience).

Whether you stay put in Paris for 6 months or travel extensively for years, it is also important to make the most of the travel itself and the places that you visit. You still need to find a balance between working to pay the bills, and budgeting time, money and energy to see the sights, taste the food, just 'hang out' with the locals and – hopefully – make new friends and some special memories. Otherwise, there is no point in going at all.

#### A final word of advice – Go!

As with any project, good planning is essential in creating a rewarding trip that doesn't turn into a nightmare, and you should plan as much as you can – particularly the legal and financial stuff. However, you will probably never be totally ready, and you won't be able to anticipate all of the problems that you will encounter – there will be times when you are way out of your comfort zone. The most important step, however, is to go. I hope that I haven't put you off!

**Sarah Smith, PhD**

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world on her yacht  
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*Sarah's husband, son, and daughter collecting coconuts on the beach in Tobago*

Image courtesy of Sarah Smith.

# Upcoming issues of **Medical Writing**



**March 2019:**

## **Careers in medical writing**

By choice or by chance? Medical writing work is very diverse and so are the careers of people in this field. This issue will focus on stories about medical writing careers.

Guest Editors: Brian Bass and Raquel Billiones

**The deadline for feature articles is December 10, 2018.**



**June 2019:**

## **Generics and biosimilars**

This issue will introduce readers to generics and biosimilars; provide and discuss their key legal and regulatory aspects in the US and Europe; and discuss their economics and how they affect pharmaceutical companies. Guest Editor: Diana Radovan

**The deadline for feature articles is March 10, 2019.**



**September 2019:**

## **Trends in medical writing**

The medical writing industry is growing and evolving at a fast pace, and we need to keep up with the trends. From public disclosure to global medical writing, find everything you need to know in this issue. Guest Editor: Somsuvru Basu

**The deadline for feature articles is June 10, 2019.**



**December 2019:**

## **Artificial intelligence & digital health**

Technological innovation is overtaking all industries, and medicine is no exception. Artificial intelligence, digital health, biohacking, and health optimisation are growing trends, and as medical writers, we must understand and communicate these advances. Guest Editor: Evguenia Alechine

**The deadline for feature articles is September 9, 2019.**

### **CONTACT US**



If you have ideas for themes or would like to discuss any other issues, please write to [mew@emwa.org](mailto:mew@emwa.org).



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