

Medical Writing



Medical decision making and health technology assessment

ALSO IN THIS ISSUE...

- The value of patient voices in plain language summaries
- Inclusive language: A hidden power at the hands of medical writers

Volume 30 Number 3 | **September 2021**



EUROPEAN MEDICAL WRITERS ASSOCIATION

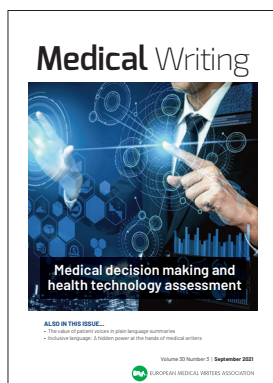


Medical Writing

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THIS ISSUE September 2021 | Volume 30 Number 3

Medical decision making and health technology assessment

“Over the last 50 years, the paradigm of medical decision making has been changing, involving a greater role for published evidence and an expansion of the clinician’s role to include both individual-level and population-level decision making.”

Michael Drummond, “The increasing role of evidence”, p. 8

Editorial: Medical decision making and health technology assessment 2
Maria Koltowska-Hägström, Claire Gudex

President’s Message 4
Carola Krause

From the Editor 5
Raquel Billiones

EMWA News 6

FEATURE ARTICLES

Medical decision making at the individual and population level: The increasing role of evidence 8
Michael Drummond

Global HTA: Past, present, and future 16
Wendy J. Babidge

Early benefit assessment of new drugs: The impact on healthcare in Germany 22
Michael Köhler, Annette Christoph

Decision-making in Slovenian outpatient care: Can financial incentives reduce patient waiting lists? 28
Valentina Prevolnik Rupel, Marjeta Kuhar, Dorjan Marušič

Patients are decision makers too 34
Angela Coulter

Quality patient decision aids to support healthcare decision making 38
Jeanette Finderup, Dawn Stacey

EUPATI: Patient engagement through education as an important contributor to shared decision making 46
Victoria Thomas

The regulatory-HTA decision-making interface: What the medical writer should know 50
Lawrence Liberty, Tina Wang

Communicating the findings of health technology assessments: Considering uncertainty 56
Jacqueline E. Parsons

Reporting health economic evaluations: CHEERS and beyond 60
Don Husereau, Chris Carswell, Michael Drummond

The medical writer’s role in health technology assessment submissions 68
Jo Whelan, Tina Krieger

HTA decision-making: Do ethics matter? 72
Art Gertel

Why would the healthcare industry need a doughnut? 76
Kate Silverthorne

Master protocol studies: Embracing the “new normal” 83
Jonathan Mackinnon, Aitana Gisbert

REGULAR SECTIONS

News from the EMA 90

Medical Devices 96
 • Clinical investigation for medical devices – types and stages

News and Notes from the World of Medical Writing 98

Regulatory Matters 99
 • Biomarkers on my mind

Veterinary Medical Writing 100
 • Comparative medicine: A view from the veterinary clinic

Medical Communications and Writing for Patients 104
 • The value of patient voices in plain language summaries

My First Medical Writing 109
 • Clinical trial management and patient recruitment in the emergency department
 • A gut-feeling: How intestinal diseases can affect our sleep

Good Writing Practice 114
 • Grammatical disagreement in voice

The Crofter: Sustainable Communications 116
 • EMWA as partner organisation in the UN Partnership for SDGs platform
 • Inclusive language: A hidden power at the hands of medical writers

Out on Our Own 124
 • Freelancing: Freedom or isolation?



Medical decision making and health technology assessment

Many of the key decisions in our lives concern our health and well-being. These decisions are often made for us at the societal level, but as individuals we have increasing say in the management of our own healthcare and in societal decisions. Having said that, welcome to this issue of *Medical Writing*, which is devoted to medical decision making (MDM) and health technology assessment (HTA). We are proud to present a wide collection of articles written by top experts and organised in four main sections:

- An overview of MDM and HTA in health care
- Shared decision making and the patient role

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- Medical writing in MDM and HTA
- Wider perspectives.

Michael Drummond opens the issue with an overview of MDM at societal and individual levels and explains the interrelationships between evidence-based medicine, comparative effectiveness research, and HTAs. In the

second article, **Wendy Babidge** describes the development of HTAs as a multidisciplinary process, compares “eminence-based decisions” to “evidence-based medicine”, particularly during the early days of the COVID-19 pandemic, and outlines the expanding “HTA community” in the form of global and regional networks established for collaboration within HTAs and sharing knowledge. Their articles are followed by two country-specific examples of MDM policies: one from Germany, presented by **Michael Köhler and Annette Christoph**, and another from Slovenia by **Valentina Rupel, Marjeta Kuhar, and Dorjan Marušič**.

The next section is on shared decision making, which relates to patient involvement



in medical decisions. **Angela Coulter** discusses patient engagement in healthcare processes, reviews existing issues in patient-doctor communication, and considers the influence of the COVID-19 pandemic. **Jeanette Finderup and Dawn Stacey** then provide a comprehensive overview of patient decision aids, including the International Patient Decision Aid Standards (IPDAS), while **Victoria Thomas** in her article introduces the European Patients' Academy (EUPATI), and their collaboration with regulatory bodies such as the National Institute for Health and Care Excellence (NICE).

The third section deals with practical issues for the medical writer when submitting documents about new medicines and reporting HTA data. **Lawrence Liberti and Tina Wang** open this section with their review of regulatory documents required in submissions for new medicines, and offer practical advice for constructing these documents and the role of the medical writer. A central feature of medical decisions is that they are made under uncertainty. **Jacqueline Parsons** explains the various sources of uncertainty in HTAs and provides advice for enhancing data transparency and trustworthiness when communicating HTA findings. **Don Husereau, Chris Carswell, and Michael Drummond** then describe the Consolidated Health Economic Reporting Standards (CHEERS) for optimising quality and transparency in reporting, while **Jo Whelan and Tina Krieger** provide practical tips for the medical writer working on HTA submissions.

Considerations on MDM and HTA would not be complete without insights into ethical issues, and these are provided in the final section by **Art Gertel** in his discussion of ethical aspects of HTA. **Kate Silverthorne** then outlines a framework for sustainable development in healthcare in the context of climate change and global warming. The features conclude with **Jonathan Mackinnon and Aitana Gisbert's** thoughts on master protocol studies, followed by the many highly relevant articles in the journal's regular sections.

We would like to express our deep gratitude to the authors who have contributed to this issue. They have not only produced thoughtful and informative contributions that will be of great interest and use to our readers but have done it with enthusiasm and engagement – and not least with timely delivery of their articles. Thank you!



Maria Kołtowska-Hägström, MD, PhD, runs Proper Medical Writing, the first Polish medical writing agency that operates globally. She has previously worked within the pharmaceutical industry for over 20 years and has an extensive track record of quality of life and patient-reported

outcomes research. She is a member of the EMWA and the European Association of Science Editors.

Claire Gudex, MBChB, MD, is an associate professor at the University of Southern Denmark, where she teaches academic writing and undertakes research in patient outcome measurement. She has previously worked at the Centre for Health Economics at the University of York, UK, and the Centre for Applied Health Services Research and HTA at the University of Southern Denmark. She has been a member of EMWA since 2011.



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President's Message

After several lockdowns, “everyday” life is beginning to return, although COVID-19 continues to be a destructive force in many parts of the world. In Germany, where I am currently located, COVID-19 cases have been rather low (with occasional worrying spikes), vaccination rates have been rising, and many restrictions have been lifted.

Nowadays I prefer to work outside, and I try to convince people to call me on the phone rather than scheduling video conferences, which too often tie me up to the computer. Often, I feel the need to be at least distantly surrounded by people and I am sure these feelings relate to many medical writers and communicators. Surely, those of you who had or still have to juggle household chores, home-schooling, and professional life will feel relieved that most countries are now progressing rapidly with their vaccination programmes.

Immunisation programmes are ethically and scientifically defensible, and societies have a significant role to play in providing vaccinations globally. It is truly time to call out for global vaccine justice. Under the umbrella of the United Nations Sustainability Development Goals (UN SDGs), select countries have committed to prioritising progress for those who are the furthest behind; however, a global effort is needed. Today, I am very happy to announce that EMWA is now a registered United Nations Sustainability Partner Organisation. With this partnership, EMWA officially commits towards ensuring healthy lives and promoting well-being for all at all stages (UN SDG 3), ensuring inclusive and equitable quality education and promote lifelong learning opportunities for all (UN SDG 4), and ensuring sustainable consumption and production patterns (UN SDG 12) (see more on p. 116).

I would like to take the opportunity to thank all medical

writers and communicators for their dedication to our profession. Some of us contributed substantially to the fast development of vaccines, which allows us to almost return to a normal life today.

However, the words I chose here are misleading. It becomes clear to most of us that there is no return to our old lives. Lives have changed substantially and with it our perception of our profession. Rather than returning to our old lives,

I suggest taking the opportunity to engage in new possibilities.

By now you have received the information that the EMWA Executive Committee (EC) again decided against a face-to-face November conference. For some of you, this might be questionable and for some of you, this might be a reasonable decision. Depending on where you are located, you might have a completely different perception of the COVID-19 situation. While

EMWA's hybrid November 2021 Conference

Hybrid Conference Day
04 Nov. 2021

Virtual Workshops
05 - 24 Nov. 2021

Potential Networking Sites
04 Nov. 2021

1 site
Face-to-Face Conference Day & Networking Event
LONDON

7 sites
Streaming of the Conference Day, Face-to-Face Networking Event

ACROSS EUROPE

Virtual Activities	Hybrid Activities	Local Networking Sites
<ul style="list-style-type: none"> Workshops Symposium Experts Seminar Series Getting into Medical Writing Freelance Business Forum Mindfulness Session Yoga Session 	<ul style="list-style-type: none"> Networking Sessions Conference Day 	<ul style="list-style-type: none"> THE NETHERLANDS* UNITED KINGDOM* FRANCE PORTUGAL* SPAIN POLAND GERMANY* SWITZERLAND*

* Confirmed September 14, 2021

From the Editor

Making responsible decisions – every day

I am writing this message, Lisbon (Portugal) just went back into a lockdown, the United Kingdom (UK) reports an increasing number of COVID-19 cases, whereas other European countries are just doing fine.

As it is very difficult for the EC to foresee where we will be in November, and we always prioritise the health of our EMWA members, we announced a new conference format for the upcoming November conference. Now is the time to take the first step into a new reality. We aim to offer our first hybrid conference. All EMWA workshops will be offered in the virtual format only. However, we aim to run a 1-day, London-based, hybrid conference day on November 4, 2021. Why London? We aim to avoid cross-country travels of EMWA members and evaluate the feasibility of EMWA hybrid conferences for which we need our UK-based Head Office support.

However, networking is a major pillar of EMWA conferences, and we would like to offer local medical writers and communicators groups the possibility of organising networking events on this day. In accordance with country-specific COVID-19 regulations, we aim to live-stream the conference day from the UK, provide local face-to-face networking opportunities, and discuss urgent topics with our local peers. If you would like to support a local networking event in your area, please get in touch with us (info@emwa.org).

Additionally, we will offer PR support for the local networking events through our newly formed EMWA Creative Team. The creative team aims to support not only conferences and networking events with promotional material but also offers the creation of visuals, infographics, and slide decks for any EMWA-related activities. If you need support for social media postings, your next article for *Medical Writing*, or for the website, please email president@emwa.org.

I hope you see the opportunities the new hybrid conference brings to EMWA and to all our members.



Carola Krause
president@
emwa.org



For me, the most difficult task of medical writing is clicking that “SEND” button. After more than 15 years in this field, the decision to send out and share a document with colleagues, regulatory authorities, even the public, is always accompanied by a knot in the pit of my stomach. This simple act comes with questions ranging from the mundane “Is this document good enough or do I need another round of QC?” to the profound “Did I write this document according to Good Clinical Practice guidelines to the best of my ability?” Decision-making is part of our private and professional lives. Should I get vaccinated? Should I quit my job and go freelance? Should I work from home? Should I share this on social media? Should I try something new?

We want to make the right choices and dichotomy looks good on paper but in practice, it is not always binary; reality is seldom black or white, yes or no.

So how do I cope with the anxiety of decision making?

- Pause. Step back if we must. Boldness and spontaneity are great but leaping without looking is irresponsible.
- Talk it over. Have a sounding board, a discussion partner(s), or a second pair of eyes to look over your document.
- Do not procrastinate. Pausing is important but putting off too long is counterproductive. Reflect but do not overthink.
- Be responsible. As medical writers and communicators, our professional decisions sometimes have some far-reaching consequences, be it on a project deliverable, corporate goals, or the outcome of a global pandemic. Acting responsibly and with integrity is therefore important.
- Forgive yourself. No document is perfect. Things can go wrong. Deviations happen. Non-compliance events occur. Keep to the quality tolerance limits but learn from your mistakes.

This issue contains articles highlighting the challenges and rewards of decision-making in the healthcare industry. The first half of 2021 marked major regulatory decisions especially in Europe. The Medical Device Regulation 745/2017 came into full force on May 26, 2021, after a 1-year postponement due to the pandemic. On July 31, 2021, the European Commission officially published and confirmed January 31, 2022, as the date of application of the Clinical Trials Regulation 536/214 and the go-live date of the new Clinical Trial Information System. At the time of writing, we are awaiting updates on Plan S, an initiative for open-access science publishing.

In the midst of all these regulatory changes, medical writers and communicators play a vital role in ensuring smooth transitions and compliance. This is where our decision-making skills will stand us in good stead.

Finally, in this issue, you will become aware of the recent decisions taken by EMWA to try something new.

- We have new special interest groups (SIGs, p. 15)!
- The EMWA Executive Committee has decided to try out a hybrid conference format (see p. 4 and p. 7)
- We have decided to give the journal a new look! We also hope to move away from using stock photos and tap into the creativity of our membership. If you have any ideas for covers of our future issues (p. 127), please reach out.

To close, we would like to thank our contributors, our guest editors Maria and Claire, and our editorial team for putting this issue together. Happy reading.



Raquel Billiones
Editor-in-Chief
editor@emwa.org



Spanish translation of the Joint Position Statement on Medical Publications, Preprints, and Peer Review

We are proud to announce the posting of our first translation of the Joint Position Statement into Spanish by Almudena Pardo Mateos and reviewed by Sabrina Silano.

Read the Spanish translation on the EMWA website:
<https://www.emwa.org/about-us/position-statements/amwa-emwa-ismpp-joint-position-statement-on-medical-publications-preprints-and-peer-review/spanish/>.

We are currently looking for translators. If you would like to volunteer, please contact Abe Shevack (aspcientist@gmail.com) or the EMWA Head Office (info@emwa.org).



First face-to-face meet-up of the Swiss Medical Writers and Communicators Group

Finally, our first meet-up took place on Saturday, August 21, 2021, in Bern, Switzerland. It was a gathering of people from different demographics but who share a common passion for health communications. Of the 12 attendees – a majority already EMWA members but some non-EMWA members too – three were freelance, and four were exploring a transition into the field. We had three attendees who got their first break at the EMWA Vienna conference in 2019, which was key in their medical writing career path. One attendee transitioned from academia to medical writing after hearing a talk by an EMWA ambassador. The experience and interests of the attendees include medical comms, editing, pharmacovigilance, regulatory writing, and consultancy. The medical technology sector was especially well-represented with four attendees working fully in the medical device sector. The meet-up was slightly dominated by female attendees, but we have been assured by the men in our group that they will be at the next one. We hope to continue this success and plan more meet-ups in the near future. We hope you will join us next time! You can find the group on [Swiss Medical Writers & Communicators | Groups | LinkedIn](#).

Raquel Billiones and Laura Kehoe

EPDP badges – have you got yours already?

Have you gained a foundation or advanced certificate at EMWA and want to prominently display it as an electronic certificate on LinkedIn, your website, and emails?

Then contact EMWA Head Office at info@emwa.org.

EMWA on Facebook

We periodically review our communication activities with the membership. In light of a changing social media landscape, we have decided to disable the EMWA Facebook group. The page will be deleted soon. Many thanks to those of you who did contribute to EMWA on Facebook over the years.

Our main social media channel is the EMWA LinkedIn Group:
<https://www.linkedin.com/groups/2717752/>.

We are looking forward to your continued contributions on LinkedIn and our other social media channels.



Plans for the November 2021 EMWA conference

Sadly, we have concluded that we will not be able to run the conference in Cascais, Portugal, in November. Our priority has to be our members' health and safety. We made this decision in light of the continuing uncertainty about the COVID-19 situation, which makes it difficult for speakers, workshop leaders, and delegates to commit to travelling to Cascais, and the tight restrictions on activities set by the venue.

This is very disappointing because we know many of you were very much looking forward to meeting other EMWA members face-to-face. HOWEVER, for November, we are planning an exciting new concept, a *hybrid conference*.

For the preliminary plan, please refer to this link: <https://www.emwa.org/news/plans-for-the-november-2021-emwa-conference/>.



The latest recipient of the Nick Thompson Fellowship Award

The Nick Thompson Fellowship Award is a recognition of service to EMWA above and beyond the regular responsibilities of the membership or elected offices. It confers lifetime free EMWA membership on the elected fellows. Fellow 2021 is **Phil Leventhal** for his outstanding contribution to *Medical Writing* as Editor-in-Chief from 2011 to 2020; we are honoured to award Phil the Nick Thompson Fellowship Award and name him Editor Emeritus of the journal.

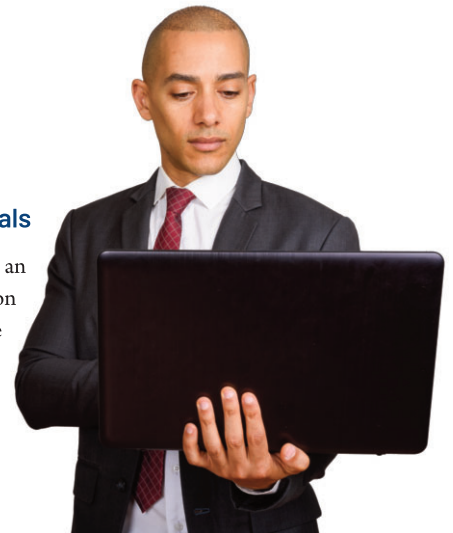
Congratulations workshop leaders!

Congratulations to **Thomas Schindler** and **Uma Swaminathan**, who have each presented 20 EMWA workshops, and to **Raquel Billiones** and **Sarah Tilly**, who have now run 10 workshops each.

EMWA web editorials

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

Explore our latest web editorials: <https://www.emwa.org/about-us/emwa-news/web-editorial/>



EMWA's contribution to sustainability

As you most likely already know, EMWA has turned its attention to sustainability in recent years. The recent founding of the Sustainability SIG is evidence of this: <https://www.emwa.org/sigs/sustainability-sig/>.

These days, there are many companies assisting associations like ours to play our part. One such company is **I Plant A Tree**. Their website contains league tables, and EMWA is currently ranked 6th in the NGO sector. We hope to plant more trees and climb even higher up the table.

6	EMWA
EMWA	10
Planted tree	0.1
CO ₂ bound (tons)	

Medical decision making at the individual and population level: The increasing role of evidence

Michael Drummond

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Abstract

The major change in medical decision making over the last 50 years has been the realisation that treatment decisions would be improved if doctors' existing knowledge was supplemented by evidence generated systematically through health services research. This paper discusses this changing paradigm and explains the related activities of evidence-based medicine, comparative effectiveness research, and health technology assessment. The latter is particularly important for making decisions on the provision of healthcare at the population level. The key steps in undertaking health technology assessments are explained, focussing on the types of literature they generate.

Introduction

When we think of medical decision making, the image that comes to mind is that of the doctor discussing with the patient, diagnosing their health condition, and then using a lifetime of accumulated knowledge and experience to determine the most appropriate treatment. Indeed, this remains the case, but over the last 50 years the paradigm of medical decision making has been changing, involving a greater role for published evidence and an expansion of the clinician's role to include both individual-level and population-level decision making.



The objective of this paper is to examine the evolving role of medical decision making, and to explore its links with comparative effectiveness research and health technology assessment. A particular focus will be the types of literature that these activities have generated, with a view to assisting medical writers in their task of producing relevant text, thereby facilitating the publication of research papers relating to these topics.

The changing paradigm of medical decision making

When doctors use their accumulated knowledge and experience to make treatment decisions, they are mainly relying on a body of evidence that is based on what they learned during their training, and the results of their previous treatment decisions. However, this knowledge is not acquired systematically, and in the middle of the last century it became clear that treatment decisions would be improved if doctors' existing knowledge was supplemented by evidence generated systematically through clinical research.

The cornerstone of clinical research is the randomised controlled trial (RCT), where in order to assess whether a new treatment does more good than harm, patients are randomly allocated to receive either a placebo or the current standard of care (the control group), or the new treatment (the experimental group). The purpose of randomisation is to minimise any biases in the assessment of comparative treatment outcomes resulting from differences in the characteristics of the patients in the two treatment groups. The main problem with studying the outcomes resulting from a new treatment in regular practice, without randomisation, is the possibility of selection bias, whereby the new therapy is given to patients who are sicker than the average or are thought to be more likely benefit from it.

Evidence-based medicine

The notion that practising physicians should be considering evidence from the literature in their decision making has become known as evidence-based medicine (EBM). There have been many thought leaders in this field, but one worth a special mention is Archie Cochrane, a Scottish physician and epidemiologist. While practising as an army medical officer in World War II, and then later dealing with the illnesses experienced by coal miners in South Wales, he realised that

randomised controlled trials were the only reliable source of evidence on whether the treatments he was giving did more good than harm.

The most important contribution of Cochrane's career was the publication of a monograph called *Effectiveness and efficiency: random reflections on health services* in 1972.¹ This book advocated the use of randomised controlled trials to make medicine more effective and efficient. Although Cochrane's main concern was with (clinical) effectiveness, he also recognised that to maximise his contribution as a physician, he also needed to consider the resources he was using. His logic was that resources, such as the doctor's own time, were limited, so that more time spent with one patient meant less time spent helping others. This raised the spectre of considering costs when making clinical decisions, which was controversial then and remains controversial today. (More on this later).

Since Cochrane's day the terminology has developed. Today we distinguish between the three E's (Box 1).

Box 1. Types of assessment of health care interventions

Efficacy: Can the therapy work under ideal conditions?

Effectiveness: Does therapy work in practice?

Efficiency: Is the therapy worth the cost?

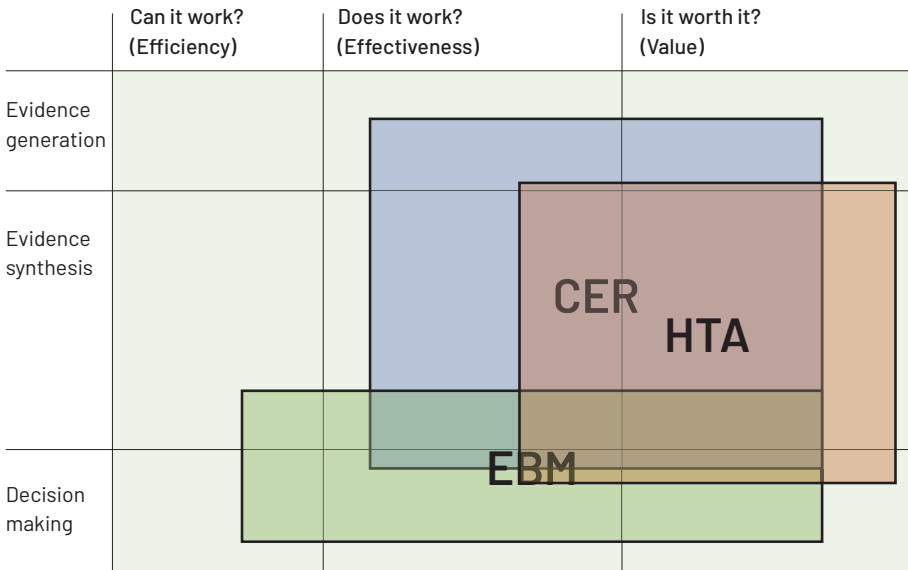
The three E's are each associated with their own set of literature. Efficacy studies are characterised by the clinical studies (normally randomised controlled trials) that are considered by regulatory health agencies such as the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) in the US. In these studies, the new treatment (such as a drug, medical device, surgical procedure, or any "health technology") is studied under ideal conditions. For example, the study may be conducted in a specialised clinical centre, the patients admitted to the study will not have any complicating co-existing health conditions other than the one for which the treatment is being given, patients and physicians will be "blinded" to the therapy to which individual patients have been assigned, and care will be taken to ensure

full adherence to the therapy.

Efficacy studies are used to investigate whether the therapy does more good than harm as bodies like the EMA assess the trade-offs between the benefit the therapy offers and its risks (i.e., the possibility of adverse events). Recent examples are the judgements made by these agencies on the suitability of the vaccines for COVID-19. However, while efficacy is important to the health agencies, practising physicians and those funding healthcare are more interested in effectiveness studies because they want to know whether the therapy works in real life settings. There are several reasons why effectiveness might not reflect efficacy: the delivery of the treatment might require expertise or resources that are not widely available, the treatment might not work as well in patients with comorbidities (which were excluded from the efficacy studies), or the nature of the treatment (e.g. complicated dosing) may cause patients not to adhere closely to the treatment regimen.

Therefore, effectiveness studies are conducted under conditions resembling regular practice. They are often randomised studies, termed "pragmatic" clinical trials, following the terminology developed by Schwartz and Lellouch.² In fact, the distinction between efficacy and effectiveness is somewhat blurred, in that clinical trials may have differing levels of pragmatism (on a spectrum from efficacy to effectiveness) depending on the setting in which they are conducted, the breadth of the patient population enrolled, the level of patient monitoring, and so on.

Many effectiveness studies are not randomised, however, because randomisation may not be possible when studying real life. Therefore, series of patients receiving different treatments may be compared in observational studies. A classic example would be the analysis of a large registry such as the National Joint Registry in the United Kingdom,³ which has enrolled thousands of patients receiving different types of joint replacements; another would be analysis of data from administrative claims databases in the US.⁴ The issue here is that since potential biases are not controlled by randomisation, it is necessary to control for potential differences between patients through the data analysis. This can involve matching approaches, such as propensity scoring, or statistical approaches involving different types of multivariate regression.⁵



- Notes:**
- EBM = evidence based medicine
 - CER = comparative effectiveness research
 - HTA = health technology assessment

Figure 1. Current confusion over the relationship between EBM, CER, and HTA.

Reprinted with permission from Luce et al.¹⁴

The success of all these analytic methods depends on the extent of information on the characteristics of patients that might independently affect the effectiveness of the therapy (e.g. age, previous treatment history, seriousness of disease, existence of other health conditions). Of course, it is only possible to account for patient differences that one is aware of, not those one is unaware of. Therefore, randomisation is in theory superior because it can minimise all possibilities of bias, although some approaches, such as the use of instrumental variables in multivariate analyses, can mimic randomised studies.⁶ For some health technologies, such as medical devices, randomised studies are rarely conducted because they may not be feasible or are not universally mandated by regulatory bodies such as the FDA. In these situations, it becomes necessary to rely on observational studies.

It follows that synthesising the results of several similarly conducted clinical trials would give more overall confidence in the result obtained and enable a more precise estimate of the relative clinical effect.

Finally, *efficiency studies* assess whether a therapy is “worth it” by comparing the benefits with the costs. As mentioned earlier, the logic for including costs is that, under conditions of limited resources, the costs represent the benefits forgone to other patients. Some clinicians find this a difficult concept and struggle with it ethically. They are used to rationing care in emergency situations, such as triage on the battlefield or dealing with the allocation of intensive care beds during a pandemic, but it is not so easy to identify the resource constraints when working in a modern, well-resourced health care system. Also, it expects the doctor to consider not only the person currently being treated but a broader population of patients, most of whom are “not in the room”.⁷ However, as will be discussed later, doctors are increasingly becoming involved in medical decision making at the

population level as well as at the individual patient level.

Efficiency studies are collectively called “economic evaluations” but generally go under the name of the particular form of economic evaluation, such as “cost-effectiveness analysis”, “cost-utility analysis”, or “cost-benefit analysis”.⁸ All the methods follow the same general methodological approach but differ in the way the benefits are measured and valued. Cost-effectiveness analysis (CEA) leaves the benefits in the clinical units of measurement, such as years of life gained, cases prevented, or disability avoided. Cost-utility analysis (CUA), also called CEA in the US literature, converts the clinical effects into a generic measure of health gain, the most well-known of which is the quality-adjusted life-year (QALY). Cost-benefit analysis (CBA) converts all the costs and benefits into monetary terms but is not very common in the health literature, owing to mixed feelings about placing a monetary value on improved health or life-years gained.

The other major development following the Cochrane era was the realisation that although a single RCT is a reliable source of evidence about the efficacy or effectiveness of a treatment, it is ultimately specific to the precise circumstances in which it was conducted. It would be even more convincing if the same finding was reproduced in several similar clinical studies. Also, the precision by which a given relative clinical effect can be estimated depends on the sample size of the clinical trial. It follows that synthesising the results of several similarly conducted clinical trials would give more overall confidence in the result obtained and enable a more precise estimate of the relative clinical effect.

This has been the motivation for conducting systematic reviews of clinical trials, or of the available clinical evidence more generally. The most important organisation that promotes the conduct and use of systematic reviews is appropriately named the Cochrane Collaboration. This has developed into a major international movement with the mission “to promote evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews and other synthesised research evidence”. The organisation’s vision is “a world of improved health where decisions about health and healthcare are informed by high-quality, relevant, and up-to-date synthesised research evidence”.⁹



Comparative effectiveness research

Finally, “comparative effectiveness research” (CER) is a term that is now in common usage in the US. It refers to any type of effectiveness study, including pragmatic clinical trials, analysis of registries, and administrative databases. A committee of the Institute of Medicine in the US has defined CER as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve healthcare at both the individual and population levels”.¹⁰

However, despite the intention to assist purchasers and policy makers, in most cases CER excludes consideration of costs. Indeed, the organisation established to fund these studies in the US, the Patient-Centred Outcomes Research

Institute (PCORI), is explicitly barred from using measures such as the QALY under the terms of the Patient Protection and Affordable Care Act (also known as “Obamacare”) and does not generally fund economic evaluations.¹¹

Making better health care decisions: the rise of health technology assessment

The discussion above indicates that both evidence-based medicine and comparative effectiveness research seek to improve medical and healthcare decision-making at the individual and population level. This is also the claim of health technology assessment (HTA), an approach that is increasingly popular in Europe and has been the subject of a major European Union (EU) joint action, the EUNetHTA project.¹² HTA has been defined as “a multidisciplinary process that uses explicit methods to determine the value of a health

technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system”.¹³ Technology” in this case is defined very broadly and can mean a drug, a medical device, a surgical procedure, a prevention programme, or a system of organising healthcare.

Luce et al.¹⁴ have explained the relationship between the three activities of EBM, CER, and HTA by categorising them according to two dimensions:

- i. the question being asked (can it work, does it work, is it worth it?) and
- ii. the main focus of the activity (evidence generation, evidence synthesis, decision making).

Figure 1 illustrates that the three activities clearly overlap although they have slightly different emphasis in respect of the two dimensions. Figure 2 presents a more definitive

distinction between the three activities and illustrates the role of many of the analytical approaches described, along with the relationships between them.

Health technology assessment is best viewed as the most over-arching activity of the three activities. It encompasses both clinical and economic assessments and although it is mostly relevant to population level decisions, it can be used at the individual patient level through a “shared decision making” approach in which the doctor discusses both the clinical and economic evidence with the patient. (See the paper by Finderup and Stacey in this issue.¹⁵) The explicit consideration of cost in shared decision making is particularly relevant in those settings, such as the US, where the patient may face a co-payment for their treatment.

The key steps in the HTA process are outlined in Box 2.

Box 2. Key steps in the HTA process

- Identifying topics for assessment
- Specifying the decision problem
- Searching for evidence
- Systematic review of the clinical evidence
- Economic evaluation
- Assessing social, legal, and ethical implications
- Formulating recommendations and implementation of policies
- Monitoring impact

Adapted from Goodman¹⁶

A full overview of HTA is given in the paper by Wendy Babidge in this issue,¹⁷ so only a brief description is given here, focusing on the studies that might be produced at each step. Topics for assessment are typically identified by several routes, e.g. recommendations for future research made by previous research studies, requests by government or other healthcare decision making bodies, or horizon scanning. Horizon scanning involves searching databases of ongoing clinical trials, the websites of technology manufacturers, and the general literature. The results of horizon scanning exercises are occasionally submitted for publication.

Since it is not possible to assess every new

technology given the resources available for HTA, priorities need to be set. The criteria most often used by HTA agencies are the anticipated clinical or economic impact of the new technology and the availability of evidence to conduct an assessment.¹⁸

The specification of the decision problem is a very important step, which is often conducted through a scoping exercise. A common framework used is called PICO. (Box 3).

Box 3. The PICO framework*

Patients/population: Which patients or populations are of interest?

Intervention: What is the new intervention or technology to be studied?

Comparison: What is/are the current alternative(s) to be compared with the new intervention (e.g. current standard of care)

Outcome: What is/are the main outcome(s) of interest?

*In some versions of the PICO framework, an “S” is added to PICO, representing study design.

In the HTA step on “searching for evidence”, the most important feature is to have an effective search strategy to help identify the published and grey literature. The search strategy is normally presented in publications of systematic reviews, along with the outcome of the search. This is typically published in the form of a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, showing the number of records/abstracts identified, the number and reasons for exclusions, and the final number of abstracts selected for full review.¹⁹

The systematic review of the clinical evidence is one of the most important steps in the whole process and is almost always published, either as a free-standing paper or as part of the HTA report. The main objective is usually to produce a summary estimate of the relative clinical effect of the intervention as compared with the comparator, through a process called meta-analysis. However, some studies only present a narrative review if it is considered that producing a summary estimate will be misleading or unhelpful. There are several important considerations in systematic review such as checking for

publication bias, assessing the quality of the included studies, and checking for heterogeneity in the studies. A good guide to undertaking systematic reviews has been produced by the Centre for Reviews and Dissemination at the University of York.²⁰

The final component of the assessment phase of the HTA process is economic evaluation. Not all HTAs contain an economic evaluation component, but this is more often the case now as issues of resource allocation and the efficient provision of healthcare are becoming increasingly important. The economic evaluation may be published as part of the HTA report and as a free-standing paper. Issues in the reporting of economic evaluations are explored in the paper by Huserau et al. in this issue.²¹

The social, legal, and ethical implications need to be considered as adoption of some technologies may require changes in legislation or may infringe upon certain religious, social, or political principles. These issues may be discussed in the HTA report but do not often generate free-standing publications.

Finally, the formulation of recommendations and implementation of policies suggested by the HTA are important steps as the whole purpose of HTA is to improve health care provision. Studies of the implementation of HTA findings and monitoring of the impact are sometimes undertaken and published as free-standing papers.^{22,23}

HTA in practice

Health technology assessment has a history stretching back to the 1970s and is now practised in a wide range of countries. Experience with HTA in various countries is discussed in other papers in this issue.^{17,24} Given the broad application of HTA, it is possible to compare the approaches used and to specify principles of good practice.

The practice of HTA varies between countries, both in the extent of its use and the methods used. For example, the UK and Canada are high users, but the US is a low user. The reasons for this are not entirely clear, but HTA seems to be more widely used in countries with a national health service or a national health insurance system. In countries like the US, with upwards of 1000 private health insurers, it is less clear that a single, centrally conducted HTA would be equally relevant in a wide range of diverse settings.

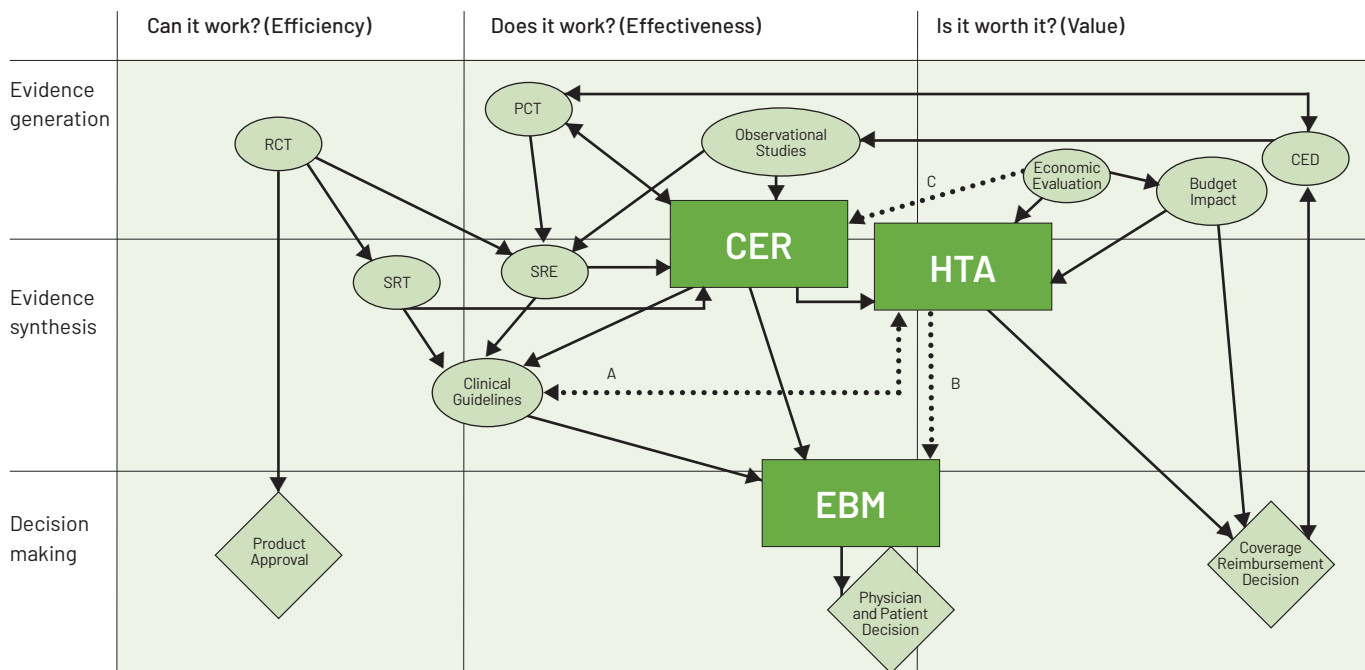


Figure 2. Redefined relationships between evidence processes and analytical approaches.

Solid lines indicate clear relationships, and dotted lines indicate disputed relationships. Diamonds represent decision processes, and circles and ovals represent all other evidence activities, except for the rectangles, which are reserved for EBM, HTA, and CER.

Abbreviations: CER, coverage with evidence development; CER, comparative effectiveness research; EBM, evidence-based medicine; HTA, health technology assessment; PCT, pragmatic clinical trial; RCT, randomised controlled trial; SRE, systematic review of evidence; SRT, systematic review of trials.

Reprinted with permission from Luce et al.¹⁴

The difference in the methods used can be illustrated by the HTA of pharmaceuticals, which has become a formal part of the approval process for reimbursement (i.e. payment by the healthcare system) in several countries. In some Northern European countries, such as the Netherlands, Sweden, and the UK, the pharmaceutical manufacturer has to produce an economic evaluation containing an estimation of the incremental cost per QALY gained from using the new drug compared with the existing standard of care. By contrast, HTA in France and Germany focuses on the “added clinical value” of the new drug, which is then used as a guide in the price negotiations between the healthcare payer and the manu-

The practice of HTA varies between countries, both in the extent of its use and the methods used. For example, the UK and Canada are high users, but the US is a low user.

facturer. Torbica et al.^{25,26} have explored whether these differences in approach can be attributed to differences in culture and values in the countries concerned or in their administrative tradition and the organisation of healthcare.

There have been several attempts to specify good practice principles for HTA. For example, Drummond et al.²⁷ specified 15 key principles for the improved conduct of HTAs for resource allocation decisions in healthcare. These were grouped according to issues in

- i. the *structure* of HTA programmes (e.g. their independence and remit),
- ii. the *methods* used (e.g. the range of costs and benefits considered),
- iii. the *processes* followed (e.g. engagement of

- stakeholder groups), and
- iv. the *use in decision making* (e.g. transparency in the link between HTA results and the decisions made).

The same group of researchers then applied these principles to a range of existing HTA programmes worldwide and developed a set of questions for benchmarking that those involved in HTA could use for self-evaluation.^{28,29} They concluded that the relevance of the various principles may vary according to the local setting and the stage of development of HTA in different countries.

Future trends

The increasing role of evidence in medical decision making is clear, both at the individual patient level (primarily through EBM) and at the population level (primarily through CER and HTA). This increase in the use of evidence has



fuelled a large increase in the published literature, primarily in the areas of systematic reviews of clinical evidence and economic evaluation. This trend is likely to continue, given the shared interests of patients, healthcare policy makers, and the general public in improving the quality of healthcare decision making. In addition, we can expect to see a geographical spread of these approaches, which are already well-established in some middle-income countries. One priority area is to make the analyses conducted as useful as possible for the decision makers concerned, which is a particular challenge in multi-payer healthcare systems such as those in the US and in several middle-income countries in Latin America and Asia.

Concluding remarks

Given the increasing role of evidence in medical decision making, the interest in published studies in this field will be from a wide range of users of this evidence, including clinical practitioners, health policy makers, and patient organisations. Therefore, this literature is not exclusively aimed at researchers who are very familiar with the key concepts and terminology used. An important role of medical writing in this field is to help authors produce work that is accessible to this wide range of users with differing backgrounds and interests.

Conflicts of interest

The author has no conflicts to declare.

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New Special Interest Groups

Welcome to our new special interest groups!



Global HTA: Past, present, and future

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Abstract

Health technology assessment (HTA) is a relatively recent innovation that has changed the way decisions are made in healthcare. It is a multidisciplinary process that requires different skill sets and collaboration among various disciplines and agencies. Evidence in the form of systematic reviews or HTAs – and more recently, overviews of systematic reviews – is increasingly being used by decision makers in healthcare globally. Key aims are to reduce duplication of effort and to provide appropriate evidence to assist people to make evidence-informed decisions about healthcare. Global and regional networks have been established to collaborate on reviews and HTAs, share knowledge, and reduce duplication. However, a very real example of inefficient evidence generation for decision making has been seen with the current COVID-19 pandemic where “eminence-based decisions” (based on the opinions of prominent health professionals) led the way early on. Hopefully, lessons can be learned from this in the future.

History of health technology assessment

Health Technology Assessment (HTA) is “a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision making in order to promote an equitable, efficient, and high-quality health system”.^{1,2}

Technology assessment began in the US in the 1970s at the Office of Technology Assessment, which amongst other areas included a Health Programme.^{3,4} This Programme was established due to concerns about the increasing costs and inefficiencies within the health system, and a desire to improve the quality of healthcare. The report on efficacy and safety of medical technologies⁴ also stressed the importance of evidence to underpin decisions for the widespread use of technologies. HTA spread to Europe in the 1970s and was first embraced by Sweden.⁵

The publication of a report in 1972 by Archie Cochrane entitled *Effectiveness and Efficiency: Random Reflections on Health Services*⁶ has served to underpin the development of HTA over the next four decades. Cochrane, who is considered the father of evidence-based medicine, stressed the importance of using data to compare the benefits and costs of alternatives when making decisions about the use of health technologies (including tests, devices, medicines, vaccines, procedures, programmes, or systems).¹ The randomised controlled trial (RCT) was recommended as the best methodology; however, it was understood that other types of evidence were useful in certain circumstances.

The first Cochrane Centre was established in 1992 in the United Kingdom, under the leadership of Iain Chalmers. Its aim was to enable collaboration on the production of systematic reviews of RCTs and to establish a register of RCTs.⁷ Cochrane Centres have subsequently been created in many other countries.⁸ This now global network has members and supporters from over 130 countries⁹ who work in a voluntary capacity supported by Cochrane Centre staff. Cochrane Collaboration evidence products are aggregated in the Cochrane Library,



There has certainly been a shift from eminence-based to evidence-based decision making, where the clinician's knowledge/expertise is used in conjunction with published research evidence, rather than despite it.



which encompasses the *Cochrane Database of Systematic Reviews (CDSR)*, the Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Clinical Answers as well as a federated search feature that incorporates results from external databases.

Why HTA is important

In his overview in this issue, Michael Drummond¹⁰ notes how medical decision making, at both the individual and population level, has changed over the past half a century. There has certainly been a shift from eminence-based to evidence-based decision making, where the clinician's knowledge/expertise is used in conjunction with published research evidence, rather than despite it.

HTA has helped support this through its focus on using evidence to support decision making at all levels of the health system, i.e. the macro policy level (structures and systems oversight), the meso healthcare level (functioning of organisations), and the micro clinical level (roles and behaviour of individuals).

With the current global COVID-19 pandemic, the importance of evidence has been highlighted by several publications in the journal *Nature*.^{11,12} Pearson¹² presented the case for quality evidence, rather than what has occurred where many poor-quality studies have been driven by the need for guidance during the pandemic. The editorial¹¹ reminds us of the required rigour of evidence and its synthesis, as well as the message that we should learn from what has happened to evidence production during the pandemic. Additionally, in the area of surgery, Kovoor and colleagues¹³ found that of studies published over a 7-month period (December 2019 to June 2020) on surgical topics relating to COVID-19, 72% had lower quality designs and 32% were opinion-based. Carley¹⁴ reported that despite a large number of trials being conducted on COVID-19, many were small and with poor design, and some had the potential for direct or indirect harm. However, there has been significant success with trials of vaccines as well as some drug treatments.

There has been a massive increase in evidence produced during the COVID-19 era, which

Network/Organisation	Established	Membership	Website/comments
INAHTA	1992	49 HTA agencies	https://www.inahta.org/
ISPOR	1995	All healthcare stakeholders	https://www.ispor.org/
HTAi ^a	2003	Individuals and agencies	https://htai.org/
EUnetHTA	2006 ^b	Organisations across 30 countries	https://eunetha.eu/
RedETSA	2011	Organisations across 19 countries	http://redetsa.org/wp/?page_id=209
HTAsiaLINK	2010	33 HTA agencies	https://www.htasialink.org/
ISPOR Regional	various	Various regional chapters	https://www.ispor.org/member-groups/global-groups/regional-chapters

Table 1. Global and regional health technology assessment networks

Abbreviations: INAHTA, International Network of Agencies for Health Technology Assessment; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; HTAi, Health Technology Assessment International; EUnetHTA, European Network for Health Technology Assessment; RedETSA, Red de Evaluación de Tecnologías en Salud de las Américas; HTAsiaLINK, HTA network of Asia-Pacific region. ^a Previously ISTAHC 1995 ^b EunetHTA Project

can make it difficult for decision makers to understand the evidence. Databases such as Epistemonikos,¹⁵ which was established in 2009, have served to support such decision making. This database contains systematic reviews and other types of structured summaries relevant for health decision-making sourced through regular screening of multiple electronic databases, including Cochrane Database of Systematic Reviews and PubMed. A search for COVID-19 on this database (May 2021) resulted in over 113,000 hits for primary studies and 7,200 systematic reviews and broader syntheses in the past year.

This highlights the need for ways to bring the best evidence from different sources together. Collaboration is key for achieving this through regional and global networks.

Global and local HTA - networks and dissemination

With this drive to incorporate the best evidence for decision making, HTA agencies have been established within governments, universities, and other institutions with the aim of generating HTAs that can inform decision making in healthcare.^{5,16}

To collaborate, network, and avoid duplication of effort, several global and regional networks have been established. Table 1 shows key examples of global and regional networks, when they were established, their membership types, and a link to their websites. Included in the table are other groups that support the HTA community, which have formed as global and regional societies. They provide networking opportunities through conferences and other educational activities. Key examples of these include Health Technology Assessment Inter-

national (HTAi)¹⁷ and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), which is a global network made up of numerous regional chapters whose aim is to develop and advance health economics and outcomes research.

These international collaborations are key to progressing the methodologies and knowledge generated from HTA producers. An example of this is the new definition of HTA^{1,2} that was created through a collaborative task group with members from the International Network of Agencies for Health Technology Assessment (INAHTA), HTAi, ISPOR, EUnetHTA, HTAsiaLink, RedETSA, and the HTA Glossary Committee.

The World Health Organization (WHO) also has a key interest in HTA, particularly in relation to its mission of achieving universal health coverage.¹⁸ The WHO resolution on HTA¹⁹ led to a call for the WHO to assess the status of HTA globally. The subsequent report found that most HTAs focus on the domains of safety and effectiveness and then economic/ budgetary areas, with much less emphasis on aspects of ethics, equity, and feasibility. For decision making, HTAs were mostly used in an advisory rather than a mandatory capacity. The report also identified barriers to using HTA in decision making, which include inadequate resourcing to conduct HTAs, lack of institutionalisation of HTA, and limited awareness of the importance

of HTA in healthcare decision making. This information has been useful as a basis to understand the current issues and needs in the area of HTA.

With this drive to incorporate the best evidence for decision making, HTA agencies have been established within governments, universities, and other institutions with the aim of generating HTAs that can inform decision making in healthcare.

Peer-reviewed publications are an important method of disseminating HTAs, which are otherwise often only available on agency or government websites. Publications indexed by global medical literature databases such as Medline and EMBASE provide easier access to publications, rather than having to trawl through the grey literature. The increasing use of Open Access and other publication models is further expanding the availability of HTA research.

Supporting the dissemination of evidence-based information are numerous academic journals that publish specifically on HTA or related to medical decision making (see Table 2 for some examples). In 2016, a journal relating to hospital-based HTA was established – the International Journal of Hospital-based HTA. In this arena, different approaches are used for HTA to guide decision making at the hospital level where the health technologies are used.²⁰ HTAi has an interest group on hospital-based HTA that maintains the AdHopHTA website and database.²¹ AdHopHTA, funded by the European Union, was a research project that developed three products for improving the practice of hospital-based HTA: a handbook of hospital-based HTA, a toolkit for setting up and running a hospital-based HTA unit, and a database of

hospital-based HTA reports. The handbook outlines the principle of hospital-based HTA, which supports the introduction of new health technologies into a hospital based on relevant, objective, comprehensive, and reliable evidence. It is provided in the specific context of the hospital where the technology is being introduced for medical decision making.

Reducing inefficiencies in the HTA process?

The globalisation and broader dissemination of HTA efforts have helped curb one of the challenges of HTA – and systematic reviews more generally – namely, the research wastage that occurs due to duplication of effort. Researchers can now register systematic reviews on PROSPERO, a database run by the Centre for Reviews and Dissemination (CRD) in the UK.²² Another useful resource, formerly produced by the CRD, is housed by INAHTA (the International HTA Database 2.0) and contains completed and ongoing HTAs.²³

EUnetHTA, a network of agencies now across 30 countries,²⁴ has developed a methodology to reduce duplication of effort and standardise the process – the HTA Core Model.²⁵ This is a framework for assessing evidence across a number of domains; it includes methodological guidance and a common reporting structure. It is available for use globally and encompasses both full and rapid assessments. The collaboration across agencies to produce a single EUnetHTA report reduces the risk of duplication of effort.

Other regional networks have the same aim as EUnetHTA of collaboration and duplication of effort; in Asia this is HTAsiaLink²⁶ with 33 member agencies and in the Americas RedETSAs, formed in 2011 across 12 countries.²⁷ HTA evidence synthesis helps make sense of the plethora of studies by assessing quality,

aggregating where applicable into a more robust evidence source, and noting gaps in the evidence base to alert researchers to priority areas for future work.

Other methodologies have been developed to improve efficiencies in the synthesis of evidence.²⁸⁻³⁰ Overviews of systematic reviews bring together data from a variety of systematic reviews to synthesise the evidence for decision making. As these methods are relatively new, there is a need for guidance for researchers who are producing overviews of systematic reviews. A mapping study of existing guidance documents by M. Pollock and colleagues²⁸ has summarised current methods and identified areas where future methodological research is required³¹ with respect to overviews. Another study by A. Pollock and colleagues²⁹ identified methodological challenges from the five exemplar overviews they assessed, and their recommendations outlined the features required in protocols for overviews. In 2019,³⁰ empirical findings were used to produce a decision tool to make informed decisions for study inclusion in overviews; this aimed at supporting researchers synthesising knowledge that includes systematic reviews. These studies support this increasingly widespread method for synthesising evidence.

A recent editorial¹¹ not only called out the failure of evidence-based medicine in a global emergency but, on a more positive note, raised the potential for automation of parts of the systematic review methodology to rapidly reduce

the timeframe for production. Examples of this include the processes for retrieving the evidence, as well as a first pass procedure for selecting the evidence. This automation will also benefit the efforts for updating systematic reviews, which is essential for keeping up with the most recent evidence, especially at the current time where the evidence is changing so quickly.

Encouraging stakeholders to use HTA

HTA has a broad stakeholder base that includes not only clinicians and governments, but also healthcare institutions, insurers, patients, and caregivers. All these groups need to make decisions about the use of health technologies.

Pearson raises the issue that despite the huge efforts to synthesise the large COVID-19 evidence base, there is no guarantee that politicians will pay attention to the evidence reports produced.¹² More broadly there are some sceptics who follow social media rather than reputable evidence sources, which is definitely discouraged.

An article by Hailey and colleagues³² reviewed literature published from 2000 to 2015 on the influence of HTAs. They found that while there was some variation in the assessed influence of HTAs, for the most part their impact was positive. Limited studies looked at clinical practice changes or changes in outcomes, and they suggested a place for clinical quality registers to fill this gap in data assessment.

There is also a move to more adaptive evidence synthesis, using real world evidence (RWE), as well as more rapid approaches, such

The globalisation and broader dissemination of HTA efforts have helped curb one of the challenges of HTA – and systematic reviews more generally – namely, the research wastage that occurs due to duplication of effort.

Journal	Established	Website
<i>International Journal of Technology Assessment in Health Care</i>	1985	https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care
<i>Value in Health</i>	1998	https://www.journals.elsevier.com/value-in-health
<i>Value in Health Regional Issues</i>	2012	https://www.journals.elsevier.com/value-in-health-regional-issues
<i>Medical Decision Making</i>	1981	https://journals.sagepub.com/home/mdm
<i>Health Technology Assessment</i>	1997	https://www.journalslibrary.nihr.ac.uk/HTA/#/
<i>International Journal of Hospital Based Health Technology Assessment</i>	2016	http://www.cybelepress.com/ijhbhta.html

Table 2. Health technology assessment journals

as rapid reviews, to make HTA more flexible and user-friendly.

There is growing interest in the use of real-world data (RWD) in HTAs, and RWE has been reported in a number of studies.³³⁻³⁶ The FDA defines these terms as follows: “RWD are data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources. RWE is the clinical evidence about the use and potential benefits or risks of a medical product derived from analysis of RWD.”³⁷ Sherman and colleagues³⁸ discuss what RWE is and how it can be used.

The RWD collected in administrative databases, registries, and other repositories has the potential to produce RWE that can be used in HTAs.³⁶ Pongiglione and colleagues³⁶ conclude that RWD, particularly related to medical devices in Europe, has the potential for use in HTAs but that there are challenges. A coordinated approach is needed to strengthen RWD production, design, and analysis. Other barriers to be overcome relate to data quality, quantity, and access. A German study³⁴ concluded that there were conflicting demands from different stakeholders (for regulators compared with HTA bodies, for example), and Facey and colleagues³³ highlighted that there is considerable collaboration needed between stakeholders to determine how RWE can be developed to inform healthcare decisions. A recent initiative was launched in the Netherlands, the GetReal Institute,³⁹ to facilitate the adoption and implementation of RWE for healthcare decisions in Europe. In the US, the FDA currently uses RWD and RWE to monitor post-market safety and adverse events, as well as for making regulatory decisions.⁴⁰ In Asia, a working group has been established (**REAL** World Data In **ASia** for **HEalth** Technology Assessment Reimbursement – **REALISE**) to develop guidance on the use of RWD/RWE for informing decision making in their region.³⁵ It is clear that there is a place for its use, but strong collaboration and organisation will be required to achieve this goal. There is a need to build research capacity for dealing with RWE and analysing observational data, which is a likely focus for HTA researchers in the near future so that they can capitalise on the potential of RWD to inform healthcare decision making.

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Although work is being done by researchers, policy makers, and regulators on expanding RWE use, patient involvement is key for the optimal use of RWE for clinical effectiveness research. The Patient-Centered Outcomes Research Institute has developed a RWE training programme, with the aim of improving patient healthcare decisions.⁴¹ The importance of public and patient involvement in HTA more broadly is covered in a recent special issue in *IJTAHC* where articles cover strategies for patient and public involvement and engagement, as well as the role of patients in decision making.⁴²

Conclusions

There is no doubt that HTA has changed the way decisions are made in healthcare, however there is always room for improvement. Recent methodological changes, such as the incorporation of real-world evidence, challenge the traditional processes for synthesising data. The HTA community is growing globally, and through this many collaborations are possible. Efforts are being made to better engage with all HTA stakeholders through both individual pursuits and an increasing number of international networks. Together as a community, we can improve the healthcare provided to our societies.

Conflicts of interest

The author is employed by Cambridge University Press that publishes the journal, *IJTAHC*, which is the journal of HTAi.

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Early benefit assessment of new drugs: The impact on healthcare in Germany

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Abstract

The early benefit assessment of new drugs was introduced in Germany in 2011. The main rationale was to support pricing negotiations between the statutory health insurance (SHI) system and the pharmaceutical industry. The early benefit assessment provides publicly available documents to inform healthcare decision makers at both population and individual levels. Besides drug pricing decisions by the SHI, the early benefit assessment contributes to other areas such as the development of clinical practice guidelines and shared decision making between the physician and patient. This article describes the process and content of the early benefit assessment, including details on the standardised dossier submitted by the pharmaceutical company, the dossier assessment conducted by the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*), and the final decision by the decision-making body, the Federal Joint Committee (*Gemeinsamer Bundesausschuss*). A case example of a dossier assessment is also presented.



The German statutory health insurance (SHI: *gesetzliche Krankenversicherung*) system is comprised of approximately 100 non-profit SHI funds.¹

About 90% of the population is insured by the SHI and is entitled to appropriate healthcare as prescribed by the German healthcare legislation (Volume V of the Social Insurance Code).² SHI funds are required to reimburse approved treatments, such as new drugs, immediately upon market authorisation, and at the same time ensure the efficient use of resources. Before 2011, their price was set solely by the pharmaceutical industry, leading to high prices for new drugs, many of which had no added benefit over established drugs.³ This changed with the 2011 Act on the Reform of the Market for Medicinal

Products (AMNOG: *Arzneimittelmarktneuordnungsgesetz*) that introduced a mandatory assessment of drugs, entitled the “early benefit assessment”.^{4,5} The main rationale for the Act was to support pricing decisions and ultimately slow the increase in drug prices.

Early benefit assessment

Competent organisations

The Federal Joint Committee (G-BA: *Gemeinsamer Bundesausschuss*) is the main decision-making body in the German SHI system. It is a council comprising representatives from SHI funds, hospitals, licensed physicians, psychotherapists, and dentists.⁶ Patient representatives contribute to discussions but do not have voting rights. The G-BA is responsible for the overall

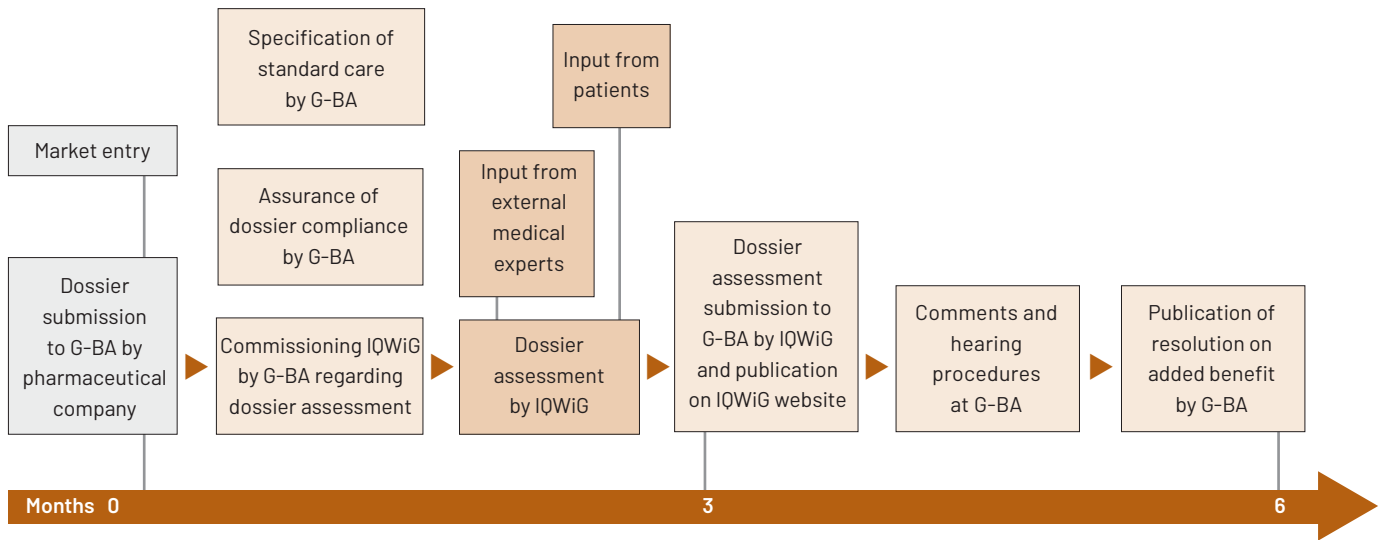


Figure 1. Stages in developing the early benefit assessment

Abbreviations: G-BA, Federal Joint Committee; IQWiG, Institute for Quality and Efficiency in Health Care

process of the early benefit assessment and for the final decision on the added benefit of a new drug.⁷ The Institute for Quality and Efficiency in Health Care (IQWiG: *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*) is a German health technology assessment agency whose main responsibility is the evaluation of drug and non-drug interventions including all new drugs (except orphan drugs). IQWiG is mostly commissioned by the G-BA.^{8,9}

Process, content, and impact of the assessment

The early benefit assessment process is a sequence of measures with clearly defined content and timelines (Figure 1).

When a new drug or an established drug with a new therapeutic indication enters the German market, the responsible pharmaceutical company must submit a standardised dossier to the G-BA containing all of the available evidence from clinical studies (preferably randomised controlled trials, RCTs).

The G-BA makes sure that the dossier fulfils formal requirements. The dossier’s scope and content are specified in a mandatory (German-language) template available on the G-BA

website^{3, 10} and consists of Modules 1 to 5 (see Figure 2). Modules 1-4 contain information on the new drug, the standard care (which is called the “appropriate comparator therapy” and specified by the G-BA), the number of patients affected, and costs of treatment. They also contain a systematic review that must show the new drug’s added benefit over standard care. Module 5 contains the corresponding clinical study reports, parts of the submission dossier for marketing authorisation, and further information.

The G-BA commissions IQWiG to assess the evidence contained in the dossier within three months after market entry; the corresponding report is called a dossier assessment (Figure 1).

Before the assessment begins, external experts and patient representatives are asked to answer questionnaires relating to the drug of interest and the corresponding therapeutic indication(s). In addition, external experts provide advice on specific issues arising during the assessment.

The assessment focuses on patient-relevant outcomes such as mortality, morbidity (including adverse events), and health-related quality of life.¹¹ IQWiG conducts a systematic review based on the approved therapeutic indication and patient

population according to the summary of product characteristics, the standard care specified, and the analysis of data on patient-relevant outcomes presented in the modules of the dossier (Fig. 2). The added benefit is determined by comparing the benefits and harms of the new drug with those of the standard care. The dossier assessment contains IQWiG’s conclusions on whether the new drug has an added benefit. The following information is provided:

1. The degree of certainty of the conclusions (from low to high: hint, indication, proof of added benefit), which is determined by the amount and quality of the study data, and
2. The extent of any added benefit (minor, considerable, major, not quantifiable), which depends on the type of outcome and the effect sizes.¹¹ This is then resubmitted to the G-BA.

Post-assessment publications and the G-BA’s final decision

The assessment process at IQWiG and the G-BA produces a number of publicly available documents (see Fig. 2). Firstly, the dossier: Modules 1-4 are published on the G-BA website. Module 5 is not published as a whole, but IQWiG may publish data in the dossier assessments as required. Secondly, the dossier assessment: The full dossier assessment is published on the IQWiG and G-BA websites 3 months after the

The G-BA is responsible for the overall process of the early benefit assessment and for the final decision on the added benefit of a new drug.

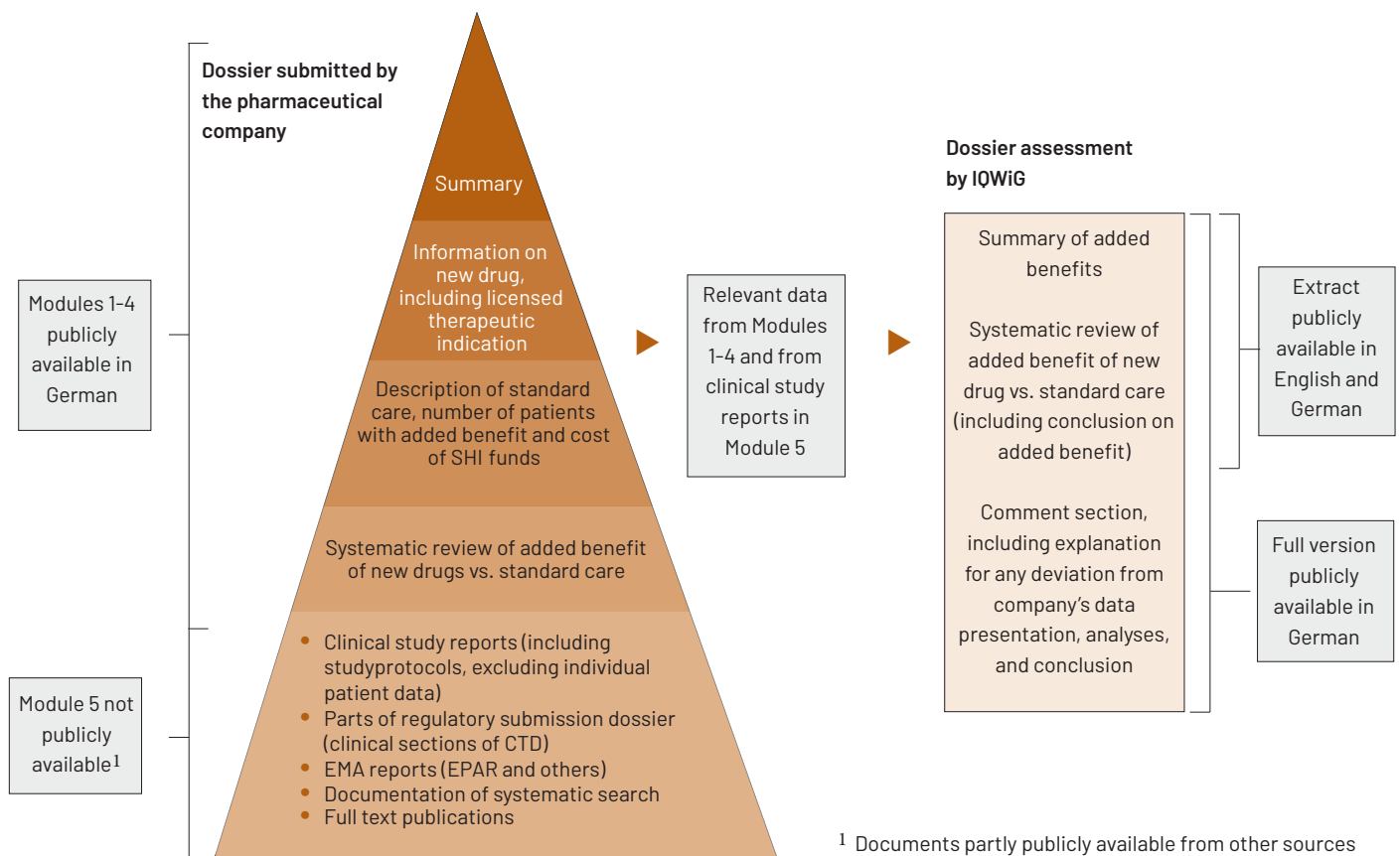


Figure 2. Structure and content of the pharmaceutical company's dossier and IQWiG's dossier assessment (modified based on Köhler et al. 2015)³

Abbreviations: CTD, common technical document; EPAR, European public assessment report; IQWiG, Institute for Quality and Efficiency in Health Care; SHI, statutory health insurance

assessment was commissioned (Fig. 1) (as an example, please see the dossier assessment on apalutamide¹²).

Thirdly, the final decision of the G-BA: This is based on the results of the dossier assessment. The dossier assessment still undergoes commenting and hearing procedures at the G-BA. Within 6 months after the drug's market entry, the G-BA publishes the final decision and a document containing the underlying reasons ("Tragende Gründe") for its decision and the comments of the involved stakeholders. These documents contain clinical data from the dossier and the clinical study reports on the studies included in the dossier assessment (as an example, please see the documents on apalutamide).^{13,14}

Post-assessment impact on different decision levels in healthcare

As intended by law or as an add-on, the G-BA's decision on the added benefit supports various decisions in the healthcare system at both

population and individual levels. The decision ultimately addresses three main stakeholder groups with different roles and needs: payers, physicians, and patients (Fig. 3).

Payers are mainly SHI funds and, to a lesser extent, private health insurance funds (as prices negotiated by the SHI umbrella organisation are also used within the private health insurance system). All new drugs are reimbursed by the SHI, but the actual reimbursement prices are subject to negotiations based on the added benefit and are determined in the final step of the early benefit assessment. Negotiations are held between the SHI umbrella organisation and the pharmaceutical company to determine the final price.⁷ No documentation on the price negotiation process is made publicly available; only the final price is published.

The conclusions on added benefit and the provision of the underlying data from the assessment process represent an additional, publicly available source of information for

physicians, who can access all public AMNOG-related documents. However, searching for and screening them can be time-consuming. To facilitate access to assessment results and to promote their use in routine care, an electronic doctor information system was launched in 2020; this system is integrated into the standard prescription software. The G-BA transfers the structured files on new drugs to the software providers who make sure that physicians can access the information swiftly.¹⁵ This tool is not meant to provide legal directives for prescribers but merely to report the evidence.

Assessment results can also be used in the development of clinical practice guidelines. Guideline developers traditionally rely on bibliographic databases as these are often the only publicly available sources of clinical study data. However, clinical study data are still not routinely available; even journal publications do not contain a full account of a clinical study.³ The situation has begun to change for newer drugs

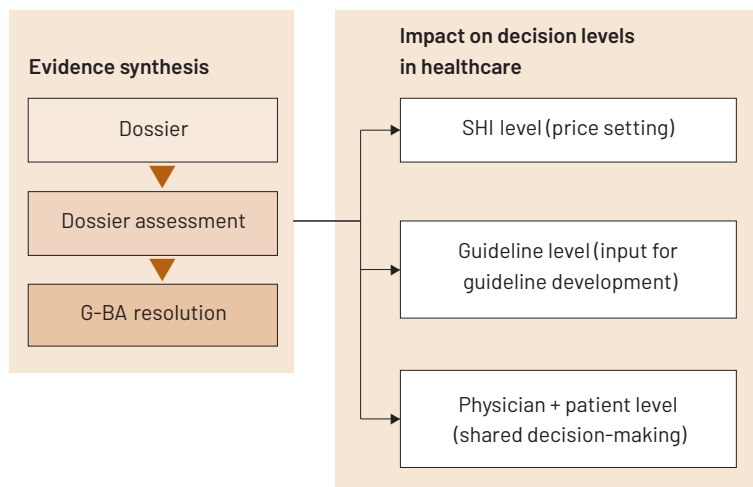


Figure 3. Impact of the early benefit assessment

Abbreviations: G-BA, Federal Joint Committee; SHI, statutory health insurance

such as through the introduced AMNOG policies and other regulatory policies, e.g. the EMA database on clinical data for marketing authorisation processes (clinicaldata.ema.europa.eu).^{16, 17} Still, there are some restrictions in the EMA database that do not apply to IQWiG. Because IQWiG has access to the full clinical study reports of all relevant studies and is free to use these data in its assessments, it adds another level of valuable information for guideline developers. This important information does not only deal with the main study results but also study methods, risk of bias and other possible study limitations, as well as additional study results

(including subgroup analyses).

Treatment decisions should ideally be made as shared decision-making between physicians and patients. It is therefore necessary to publish the findings from dossier assessments in an easily understandable format. This is in line with IQWiG's legal remit to provide health information on diseases of major epidemiological importance, diagnostic procedures, and treatments.¹⁸ This type of information, including the results of all dossier assessments, is published on the IQWiG health information website *gesundheitsinformation.de* (English version: *informedhealth.org*).

Conclusion

The process of early benefit assessment in Germany provides publicly available, comprehensive information – in both scientific and easily understandable formats – on the added benefit of new drugs. The assessment often includes previously unpublished data. Besides informing pricing decisions, further goals are to contribute to the development of clinical practice guidelines and to shared decision-making by physicians and patients.

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Conflicts of interest

The authors are employed by the Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany.

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The case of apalutamide: An example

Apalutamide is an antiandrogen used in the treatment of castration-resistant prostate cancer with a high risk of metastasis; its early benefit assessment was published in 2020.^{12–14} The G-BA defined watchful waiting as standard care (while maintaining ongoing conventional androgen deprivation therapy in both study groups). The pharmaceutical company identified only one relevant randomised controlled trial (RCT), a finding that IQWiG confirmed. The patient-relevant outcomes investigated included overall survival, symptom progression, health status, health-related quality of life, and adverse events. Apalutamide showed more favourable effects, especially on overall survival, serious or severe symptoms, and some adverse events. For other adverse events, standard care showed more favourable effects. Since apalutamide showed an added benefit for overall survival, the unfavourable effects did not offset the favourable ones. IQWiG thus concluded that the data provided an indication of a considerable added benefit of apalutamide.



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Decision-making in Slovenian outpatient care:

Can financial incentives reduce patient waiting lists?

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Abstract

Between 2015 and 2020 in Slovenia, many incentives were introduced by the main payer to increase access to outpatient health services and limit the fast-increasing number of patients waiting. Incentives oriented towards high productivity did not result in better access or improve the service mix produced. The introduction of incentives always came late in the year, because of the long process of reaching an annual general agreement, limiting their effectiveness. To increase access, the minimum number of first visits per provider needs to be defined; the amount that the provider receives for the first visit (the price) must also be increased, and the monitoring of service mix and the number of patients waiting is recommended.

Introduction

Inefficiencies in healthcare systems that result in long waiting times for doctor visits, and especially specialist visits, are challenges faced by many countries. In this article, we share the Slovenian experience relating to these challenges. Health services in Slovenia are financed through a mandatory insurance programme – the Health Insurance Institute of Slovenia (HIIS) – and voluntary health insurance premiums. An annual general agreement (GA), defined by stakeholders in the healthcare system (providers, users represented by HIIS, and the

regulator), specifies the volume and price of healthcare services to be reimbursed by the HIIS. Current payment mechanisms consist mostly of prospectively defined capped payments with retrospective realisation.

Outpatient specialist services feature highly in debates about financing, bundled payments, and shifting focus from inpatient to outpatient care; however, the effectiveness of financing and incentives in outpatient services is rarely analysed and presented. The services provided in outpatient care are paid on a fee-for-service basis, and the size of payment depends on the planned (and achieved) number of *points*. Each clinical specialty has a defined set of services (short visit, expanded visit, ultrasound, etc), and each service is assigned a cost weight expressed in the number of points. These points reflect the labour costs (medical specialists, nurses, administrative and laboratory staff), material costs, depreciation,

and healthcare service's informatisation costs. The number of services differs between specialities. For example, there are:

- 68 services in cardiology
- 79 in pulmonology
- 85 in orthopaedics
- 86 services in neurology.

The number of services has been increasing steadily; 16 new services have been added in the last decade.¹ In fee-for-service systems, financial rewards are directly connected to productivity, and the goal of providers in Slovenia has been to achieve the planned number of points defined in the annual plan.

We would expect the number of patients waiting for outpatient specialist services to be low because of the focus on high productivity. However, waiting times and the number of patients waiting for health services have been increasing constantly for the last 10 years (Figure 1).

The legal framework for monitoring waiting times was established in 2008 by the Patient



Rights Act² and the Regulation on maximum waiting times for individual health rights.³ The policy regulates the referral rules, cancellation of appointments, ranking of patients according to urgency, maximum waiting times, and the reporting rules. Maximum permissible times are defined that vary depending on assigned degrees of urgency, which are categorised into urgent, very fast, fast, and regular. The maximum permissible time is up to:

- 24 hours for urgent
- 14 days for very fast
- 3 months for fast
- 6 months for regular degree of urgency.

On May 1, 2011, the National Institute for Public Health (NIPH) published data on waiting lists for selected healthcare services for the first time. There were 24,819 patients waiting for 60 defined services. The list of 60 services was slightly changed on September 1, 2012, and then there were no further changes until May 1, 2016, when one more service was added to the list. In August 2018, the whole operational system of reporting was replaced, with changes made to the list of services, their coding, and the reporting methodology; 60 services from the previous system now correspond to 400 new services. The service code translator has not yet been officially published; however, the data could potentially be compared if it existed.

Between January 1, 2015, and January 1, 2020, the number of patients waiting for their first visit increased by 54%. On January 1, 2020, there were 403,811 patients on waiting lists, of whom 41% waited longer than the maximum permissible time. The majority, 71% of all patients, were waiting for outpatient specialist services, and the rest were waiting for diagnostic procedures or day care. The estimated financial value of services for patients on waiting lists was 120.4 million EUR, and the estimated value of service provision for patients waiting longer than the maximum permissible time was 44.7 million EUR.⁴⁻⁶

The aim of this study was to investigate the effect on waiting lists in three clinical specialties of introducing new health policies in the form of various financial incentives.

Methodology

The administrative data on the number of patients waiting for three selected outpatient specialties – orthopaedics, cardiology, and neurology – were obtained from a publicly accessible database at the NIPH.⁶ We calculated the number of patients waiting between January 1, 2015, and January 1, 2020. At the same time, we analysed the fund allocation mechanisms and financial incentives for the providers of outpatient health services to shorten the waiting lists between 2015 and 2019. The data on service

plans and production were officially obtained from administrative HIIS databases.⁷

The period 2015–2020 was chosen because of the many financial incentives introduced by HIIS during this time in an attempt to increase access to services. The waiting lists comprised mainly patients waiting for their first specialist visit after referral from primary care.

Our analysis focused on the three hospital specialties because of the large volumes of provided services and because the payment structure had not changed within the last decade.

Results

The total number of patients waiting for outpatient services in the three selected specialties was 28,516 on January 1, 2015, and increased by 34% to 38,328 patients by January 1, 2020. In the same period, the number of patients waiting longer than the maximum permissible time increased from 1,657 to 16,350, or by almost 10 times (Figure 2). This increase is much larger than the increase in the number of all the patients waiting. We saw some differences between specialties; in cardiology, where a long waiting time can have fatal consequences, the increase in the number of patients waiting was lower than in the other two specialties.

The first measure introduced in 2015 tried to implement more flexibility in the payment for first visits (Table 1). If providers provided more

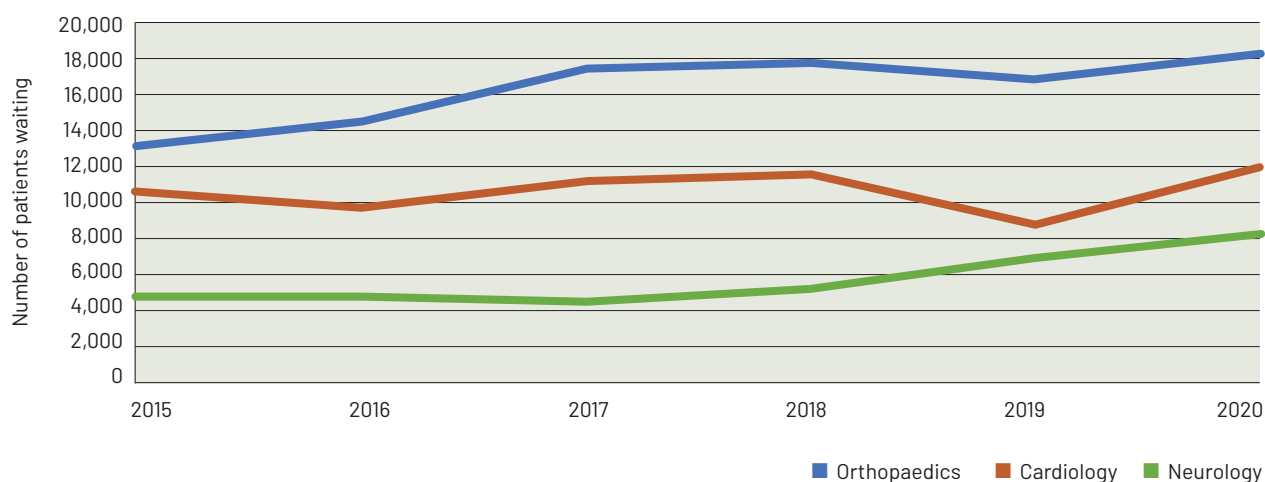


Figure 1. The number of all patients waiting for specialist outpatient services from January 1, 2015, to January 1, 2020

Source: Monthly Waiting Time Reports, National Institute for Public Health, 2015–2020.

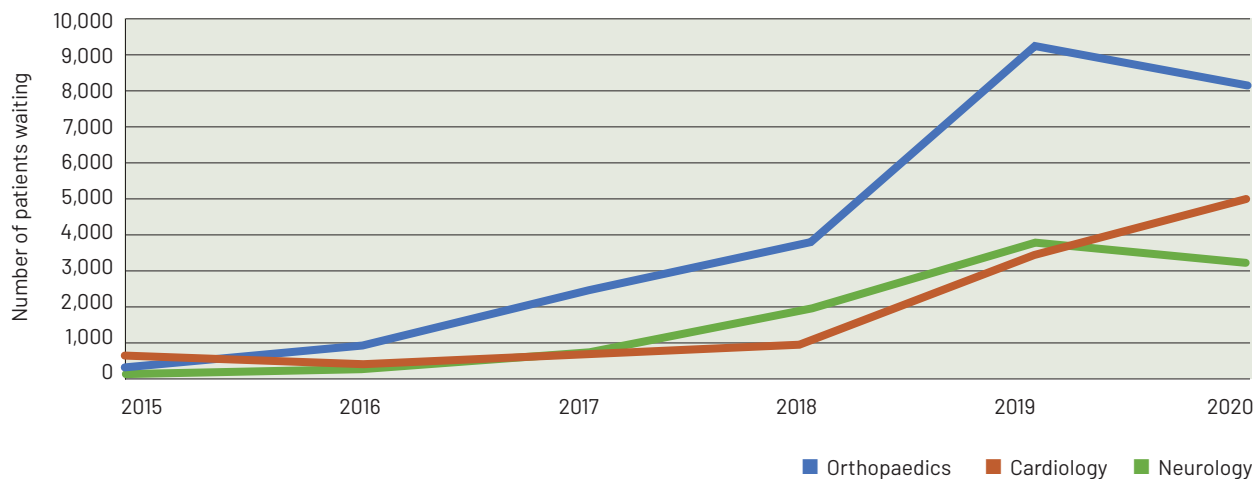


Figure 2. The number of patients waiting longer than the maximum permissible time for specialist outpatient services from January 1, 2015, to January 1, 2020

Source: Monthly Waiting Time Reports, National Institute for Public Health, 2015-2020.

first visits than planned, these were also paid for by the HIIS with the hope that providers would have greater incentive to perform more first visits and thus shorten the waiting lists.

We found that in 2015, when the providers were paid for 20% and later 10% of visits above the plan, the expected increase in number of first visits was not achieved in any specialty (Table 2). The reaction of providers to this incentive was minimal. The main reason was the retrospective nature of the measures: they were introduced in June and December 2015 and were valid for the whole year of 2015 – but the providers could not adjust quickly enough to achieve more visits when they only had 6 months or 2 weeks left in the year. The impact of the measure was, therefore, negligible.

HIIS then decided in 2016 to increase first visits further by paying for an unlimited number of them. However, except in cardiology, the number of first visits continued to decrease (Table 2), and the number of persons waiting continued to increase. The problem was again the retrospective nature of the incentive as it was introduced in June but valid for the whole year. In all three specialties, the number of points increased, indicating that the providers followed their primary goal (to achieve the planned number of points defined in the annual plan). While the number of visits decreased, providers performed more procedures per visit to reach the points outlined in the plan.

In 2017, the HIIS introduced another new measure that focused solely on points; they

decided to pay 20% of the points above the plan. As observed from Table 1, the number of points did increase and was higher than the plan, but it also resulted in fewer first visits because of the formula used by the HIIS to define the plan of first visits.*

In 2018, despite 3 years of additional measures and incentives, the planned and achieved numbers of first visits were lower (or the same for cardiology) than in 2015. The HIIS, therefore, decided to introduce a slightly different and potentially very efficient measure, where a minimum number of first visits was defined and specified separately for each medical specialty and each provider, alongside an additional payment of 20% of all points achieved above the plan. At the same time, the HIIS increased the

Table 1. Financial incentives introduced by HIIS to increase patient access, 2015 – 2019

Source: Health Insurance Institute of Slovenia, General Agreements (GAs) 2015–2019

GA or annex	Incentives	Acceptance date	Starting date (all retrospective)
GA 2015	Payment of 20% above the plan for first visits	6/24/15	1/1/15
GA 2015	Payment of 10% above the plan for first visits	12/16/15	1/1/15
GA 2016	All first visits paid	5/19/16	1/1/16
GA 2017	Payment of 20% above the points plan	6/21/17	1/1/17
GA 2018	All first visits paid, separate plan for first visits	1/31/18	1/1/18
GA 2018 Annex 1	Payment of 5% above the points plan	6/14/18	1/1/18
GA 2018 Annex 2	Payment of 20% above the points plan	10/18/18	1/1/18
GA 2019	Payment of 5% above the points plan	2/21/19	1/1/19
GA 2019 Annex 3	Payment of 15% of the excess in number of points	10/24/19	1/1/19

Table 2. Number of first visits (planned and realised), number of follow-up visits, and number of points (planned and realised) provided in three selected specialties, 2015–2019

	No. of first visits (planned)	No. of first visits (realised)	No. of follow-up visits	Points (planned)	Points (realised)	No. of first visits (realised/ planned) as percentage	Visits (follow-up/ first)	No. of points per visit
Cardiology								
2015	50,174	48,551	147,169	3,950,820	3,801,165	96.8	3.03	19.4
2016	48,813	48,923	148,528	3,810,532	3,844,380	100.2	3.04	19.5
2017	48,398	48,800	142,699	3,803,317	3,881,774	100.8	2.92	20.3
2018	48,563	50,729	137,554	3,818,933	3,881,979	104.5	2.71	20.6
2019	76,072	52,862	133,020	3,937,509	4,048,606	69.5	2.52	21.8
Orthopaedics								
2015	104,578	98,723	85,317	1,585,015	1,291,305	94.4	0.86	7.0
2016	109,650	96,602	88,600	1,516,722	1,273,570	88.1	0.92	6.9
2017	106,982	97,341	89,080	1,505,127	1,297,553	91.0	0.92	7.0
2018	103,109	91,276	85,153	1,460,839	1,247,562	88.5	0.93	7.1
2019	113,465	93,753	89,819	1,482,507	1,373,983	82.6	0.96	7.5
Neurology								
2015	42,248	39,033	32,256	2,418,462	2,359,742	92.4	0.83	33.1
2016	34,450	10,878	32,727	2,339,447	2,445,315	31.6	3.01	56.1
2017	32,485	26,710	30,591	2,312,721	2,409,178	82.2	1.15	42.0
2018	36,267	27,762	28,378	2,356,657	2,420,869	76.5	1.02	43.1
2019	27,606	30,339	28,513	2,308,696	2,408,161	109.9	0.94	40.9

Source: Health Insurance Institute of Slovenia database, 2015–2019

price (by increasing the point value) of first visits by 10%. All first visits were paid. This measure went into effect in January 2018 and had the potential to substantially reduce the number of patients waiting.

However, the minimum number of first visits was calculated according to an undisclosed formula, which resulted in increased plans for first visits according to the national average, but which were impossible to achieve for most providers (except for tertiary clinical centres). There was widespread opposition to the proposal among healthcare providers and, by June 2018, Annex 1 to GA 2018 had already abolished the obligation of minimum first visits. The number of achieved points again became the only incentive and obligation for the providers.

Discussion

Although outpatient services represented 12% of the total expenditure for healthcare services in Slovenia in 2019, there is currently no published analysis of the effectiveness of the financial mechanisms in outpatient care. From our analysis of specialist outpatient services in three clinical areas, it is clear that the quantity of services provided per team is too low despite the possibility to achieve more points and thus receive more funds. However, the question of the structure of the planned package remains open. Long waiting lists indicate too few first visits.

The incentive of financing points above the agreed annual plan is, for Slovenia, not only ineffective but actually damaging.

The decision-making about the introduction of incentives should be based on carefully analysed data. The incentive of financing points above the agreed annual plan is, for Slovenia, not only ineffective but actually damaging. The providers chose to achieve the planned number of points by increasing the number of procedures (e.g., ultrasound) per visit. For example, the first visit in cardiology had an almost five-times lower value than the request for an ultrasound of the heart. In such a situation, the decision by providers not to opt for

more first visits but to produce more services per visit is understandable. The analysis showed that the number of all specialist visits (first and follow-up) decreased continuously: between January 1, 2015, and January 1, 2020, the number of visits in the three specialties decreased by 5%. At the same time, the number of points increased by 5%, indicating an increase in the number of services per visit. Curbing the number of services per visit would require an analysis of the added value of the services provided and the measurement of

* The plan of points is fixed as described in the introduction. When HIIS defines the plan of first visits for each provider or team, the fixed plan of points is divided by the average realised number of points per first visit. Logically, if the provider provided fewer first visits or more points in the previous year, this would result in more points per first visit and fewer planned first visits. This core flaw in the system reduced accessibility and diminished the effectiveness of all the incentives that were introduced with the aim to increase the number of first visits and shorten waiting lists.



patient-reported and clinician-reported outcomes.

The incentive to pay for points above the plan should have had a positive impact on the number of first visits and hence given higher access to healthcare. However, because of the formula used, increasing the number of points resulted in fewer planned first visits. The payment for additional first visits barely compensated for this flaw and did not increase the number of first visits to the level required.

The incentive to focus on financing all first visits was equally ineffective in these circumstances, where the providers did not even achieve the planned number of first visits; it also sent a mixed message to the providers, especially in combination with the relatively low price for the first visit. The benefit of the incentive simply could not outweigh the additional effort required to catch up or exceed the planned number of first visits, and so was not adopted by the providers.

Based on the results of this analysis, the approach for 2021 has been changed. The planned number of first visits will be based on the achieved number of first visits in the previous year plus the number of patients waiting longer than the maximum permissible time. Needs defined in this way have then been divided across the available teams in each medical specialty. The increase in the first visit price will be combined with the defined minimum number of first visits per provider. Teams with patients waiting longer than the maximum permissible time and at the same time providing fewer first visits than planned will lose part of their budget, reflecting the difference between the planned and

The benefit of the incentive simply could not outweigh the additional effort required to catch up or exceed the planned number of first visits, and so was not adopted by the providers.

achieved number of first visits.

The current optimisation of access to specialist outpatient services follows the needs of the population and is related to demographic and epidemiological trends and clinical developments. In the future, it will be necessary to increase or adapt the number of medical teams based on the age structure of the population and the disease burden. Financial incentives should be introduced to produce more first visits with a commitment to achieving at least the national average, combined with the monitoring of waiting lists and, finally, encouraging standard treatments for patients with comparable diagnoses.

Conclusion

The incentives in outpatient care between January 1, 2015, and January 1, 2020 in Slovenia were all oriented towards higher accessibility but instead resulted in steeply increasing numbers of patients waiting for first visits. The incentives introduced by the HIIS were unsuccessful, because they were incorrectly oriented towards higher productivity of outpatient services, rather than incentivising an appropriate structure of outpatient care. The current incentives, in the form of a separate plan for first visits and higher prices for first visits, should reduce the number of patients waiting and ensure faster access to outpatient care for patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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Patients are decision makers too

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Abstract

Involving patients in decisions about their care attracts wide support in theory, but making it happen in practice has proven quite difficult. Embracing shared decision-making with patients will be more important than ever when healthcare organisations emerge from the COVID-19 crisis and must face the inevitable backlog of unmet health needs.

Shared decision making

“Build back better” is the oft-heard plea from those hoping that something good will emerge from the COVID-19 crisis. Medical decisions made without the involvement of patients is one area that is ripe for improvement, but shared decision-making has been conspicuously absent during the pandemic. Why does this matter, and what can be done about it?

Prior to the pandemic, the requirement to inform and involve patients was moving up the policy agenda in many countries, with governments, health authorities, and professional bodies espousing more collaborative models of care, encouraged by patient advocates. Examples were beginning to emerge on what could be done to encourage a more equal relationship between patients and clinicians by involving patients in decisions about their care. Case studies from several countries underscored the importance of effective leadership, appropriate infrastructure, training, and practical demonstrations to encourage collaboration and partnership.¹

It felt as if real progress was being made, but then along came COVID-19 and the mood changed. On the advice of public health experts, governments adopted a directive, authoritarian approach to dealing with the emergency, laying down rules of behaviour to prevent the spread of the virus. While this abrupt change represented a rational and probably unavoidable response to

the crisis, it was a major setback for advocates of patient and public involvement, especially when autocratic patterns of decision-making were replicated in the clinic or by the bedside.

Too often, doctors tell patients what they have decided to do – instead of laying out the options and asking the patient which they would prefer. This is the response of clinicians trained to believe they are the only expert in the room and are uniquely qualified to decide on the best treatment. In doing so, they ignore vital information essential to good decisions, namely the patient’s knowledge of their own situation, their experiences, and their values. A medical condition can usually be treated in more than one way, so it seems obvious that patient’s views and preferences should be sought. The result

otherwise is poor-quality decision-making, less adherence to recommendations, and more unwanted, inappropriate care.

Patients who are actively engaged in the decisions about their condition feel more responsible and motivated to cope with their disease; this, in turn, improves compliance and adherence, and thus also treatment outcomes.

Shared decision-making is the antidote to this. It is a process in which clinicians (doctors, nurses, therapists, and other health professionals) and patients work together to select tests, treatments, prevention strategies, or support packages, based on clinical evidence and the patient’s informed preferences. It involves asking patients about their experiences, listening actively, providing them with information about all feasible options, eliciting their preferences, and jointly agreeing on a plan of action. The aim is to help patients engage in a deliberative process, enabling them to





understand, think about, and weigh up the balance between likely benefits and harms of the different options.

For major or complex medical decisions, the process can be supported by the use of patient decision aids. These are evidence-based information packages outlining likely outcomes and uncertainties. They can take several forms, from brief summaries designed for use as conversation aids in medical consultations to more detailed booklets, websites, or videos for the patient to review at home. Such tools are available to support decision-making for many of the most common medical conditions, and their effectiveness has been demonstrated in numerous studies.² Most patients find this type of well-designed information helpful, including those from disadvantaged groups who are especially likely to gain benefit from it.³

Shared decision making can also strengthen people's capacity to manage long-term conditions. Evidence suggests that a collaborative

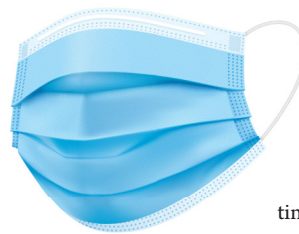
approach to care planning – learning about an individual's concerns, finding out what changes they feel able to make, and supporting them in doing so – leads to improvements in their physical and emotional health and their self-management capabilities.⁴ Patients who are actively engaged in the decisions about their condition feel more responsible and motivated to cope with their disease; this, in turn, improves compliance and adherence, and thus also treatment outcomes.

Making it happen

Shared decision-making draws together two of the major goals of modern healthcare – evidence-based medicine and person-centred care – into a pinnacle of excellence that many aspire to.⁵ Recommended more than 30 years ago by a US Presidential Commission, shared decision-making was seen as a way to reform doctor-patient communications and make informed consent more meaningful. It explicitly recognises that clinicians and patients bring different, but equally important forms of expertise to the decision-making process. The clinician's expertise is based on knowledge of the diagnosis, likely prognosis, treatment and support options, and the range of possible outcomes, while the patient has expert knowledge of the impact of the condition on their daily life and their personal attitude to risk. Good-quality decisions draw on both types of expertise.

This approach is now widely recognised as relevant for people facing major treatment decisions when there is more than one feasible option, for decisions about screening tests and preventive strategies, for diagnostic decisions, for maternity care choices, for setting goals and developing action plans in relation to long-term conditions, for advance care planning for mental health problems, and for end-of-life care. However, despite its many advantages, the uptake of shared decision-making into mainstream care has been slow and highly variable.

A disturbing consequence of the health crisis is the fact that much of the care needed by patients with non-COVID conditions was halted, delayed, or went online, causing a huge backlog and lengthening waiting times that will take several years to work through.



Most people want to be involved in decisions about their care, but their opportunities to do so are often thwarted by clinicians unwilling, or unable, to cede control.⁶ It is quite common for doctors to do most of the talking instead of listening to patients and responding to their concerns. Others believe they practise shared decision-making when in fact they don't – or think their patients don't want it when in fact they do. It is true that some patients who are used to a

more paternalistic style are surprised when they are expected to play an active part. They may need preparation and encouragement for this role, but the essential point is that this should be a *shared* process and not a delegation of responsibility to the patient.

Many clinicians believe that informing patients about options for treating or managing their conditions, asking about their preferences, and making decisions together takes far too long and cannot be accommodated within a standard consultation. Yet the evidence refutes this, showing it does not have to be burdensome if it is well-supported.^{7,8}

Dealing with the post-pandemic backlog

A disturbing consequence of the health crisis is the fact that much of the care needed by patients with non-COVID conditions was halted, delayed, or went online, causing a huge backlog and lengthening waiting times that will take several years to work through. The pandemic has also brought the shocking nature of health inequalities to the forefront of public awareness, and the unfair burden of ill-health borne by those in the most vulnerable groups, can no longer be ignored. Dealing with this reservoir of unmet need will require building a public consensus on health priorities, doing everything possible to eliminate unnecessary treatments, and providing effective support for self-care.

Whether it comes from leaflets or newspapers, much published health information has tended to present a biased, uncritical

perspective on the benefits of medical care.⁹ This leads both patients and professionals to overestimate the benefits and underplay the harms of medical interventions.^{10,11} This fuels the demand for unnecessary treatments, for interventions that prioritise longevity over quality of life, and for screening programmes that promise early diagnosis of conditions that cannot be cured or may not require treatment. In the post-pandemic world, the aim should be to correct this imbalance to ensure that a better-informed public will be more critical of false promises and less tolerant of clinicians who fail to involve them or ignore their views.

Providing access to reliable, evidence-based information about treatment options, benefits, harms, and uncertainties and ensuring that this informs discussions between doctors and patients are key steps in the path to high-value care. It has been shown to produce more realistic expectations and greater congruence between patients' values and treatment choices.¹² Informed patients often modify their expectations and opt for less aggressive interventions when they have a better understanding of the trade-offs between benefits and harms. Examples include reductions in rates of elective surgery and less use of unnecessary antibiotics.^{13,14} A large US trial found that supporting patient involvement in treatment decisions resulted in fewer hospital admissions and fewer elective procedures, leading to an overall reduction in medical costs.¹⁵

Redoubling efforts to promote more collaborative relationships in which decisions are shared between clinicians and patients should be a central focus of efforts to build more resilient health services in the aftermath of the COVID-19 pandemic. This is what is needed to set us on the path to enhanced self-care and less dependence, fewer inappropriate interventions, more effective prevention, improved targeting of resources on those with the greatest needs, and better health outcomes.

Conflicts of interest

The author declares no conflicts of interest.

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Quality patient decision aids to support healthcare decision making

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Abstract

This article describes the development and use of quality patient decision aids to support patient involvement in making healthcare decisions. Briefly, patient decision aids should provide at least information on options, benefits, and harms, and help patients clarify their values for outcomes of options. The International Patient Decision Aid Standards provide guidance on developing, evaluating, and implementing quality decision aids that minimize the risk of biased decision making. Combining these standards with the related Standards for UNiversal reporting of patient Decision Aid Evaluation studies (SUNDAE), authors of articles on patient decision aids can ensure clear, concise, and understandable reporting.

Quality patient decision aids to support healthcare decision making

What are patient decision aids?

Over the last 20 years, many health authorities and healthcare organisations around the world have encouraged providing healthcare that is more centred on patients and their families.^{1,2} Patient-centred care provides “care that is respectful of and responsive to individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions.”³

Patient participation in clinical decisions can, however, be slowed by certain barriers. In particular, patients need to know about their condition and the treatment options and outcomes (benefits, harms); know their personal values and preferences; and believe that they can influence decision making, for example, that they have permission to participate, are confident in

their knowledge, and effective at applying their decision making skills.⁴

Patient decision aids are designed to help patients overcome these barriers and participate more actively in healthcare decisions. A patient decision aid can be defined as:

“An aid that supports patients by making their decisions explicit, providing information about options and associated benefits/harms, and helping clarify congruence between decisions and personal values.”⁵

Patient decision aids are available in a variety of different formats, including leaflets, videos, and internet-based tools. Patients can use them before, during, or after face-to-face meetings with their health professionals, or they can use them on their own without any connection to a health professional.⁶ The largest database of patient decision aids is Ottawa Hospital Research Institute’s A to Z Inventory of Patient Decision Aids.⁷

A Cochrane review of 105 randomised control trials⁵ showed that patients exposed to patient decision aids had more knowledge about treatment options, more realistic expectations, less decisional conflict related to feeling uninformed or uncertain about personal values, and more involvement in the decision-making process than patients receiving standard care

only. Patient decision aids also reduced the number of patients choosing major elective invasive surgery in favour of more conservative options. Hence, patient decision aids overcome several of the barriers patients have in participating in decision making⁴ by increasing knowledge of the condition, options, and outcomes; clarifying patients’ values; and providing a structured approach to making decisions.

What is IPDAS?

Patient decision aids can improve uptake of treatment options. This is good when the changes are due to patients’ understanding or when patients’ values are acknowledged. But this is not good when it is caused by the potential for bias. ⁸ A concern has been the potential for bias in patient decision aids intended to increase the uptake of specific options.

To help address this, in 2003, an international collaboration of researchers and key stakeholders (patients, healthcare professionals, and policy makers) developed the International Patient Decision Aids Standards (IPDAS), which are a set of criteria to ensure the quality of the content, development, implementation, and evaluation of

patient decision aids.⁸ In 2013, the evidence informing IPDAS was updated⁹ and the original 74 IPDAS criteria were further revised into a minimum set of 44 criteria,¹⁰ including six items defining what is a patient decision aid, 10 items intended to minimise the risk of bias, and 28

items indicating the quality of a patient decision aid but whose omission would not present a high risk of harmful bias (Table 1). The IPDAS criteria have been adopted by the Washington State Health Care Authority for their programme to certify patient decision aids¹¹ and by the Norwegian Department of Health for approval of patient decision aids.¹² Further, all patient

decision aids in the Ottawa Hospital Research Institute’s A to Z inventory have been assessed using the IPDAS criteria.⁷

A concern has been the potential for bias in patient decision aids intended to increase the uptake of specific options.

“Dialysis Choice” – an example of a patient decision aid designed to meet IPDAS criteria

“Dialysis Choice” (Figure 1) is an example of a patient decision aid designed to meet the IPDAS criteria and is included in Ottawa Hospital Research Institute’s A to Z inventory of Patient

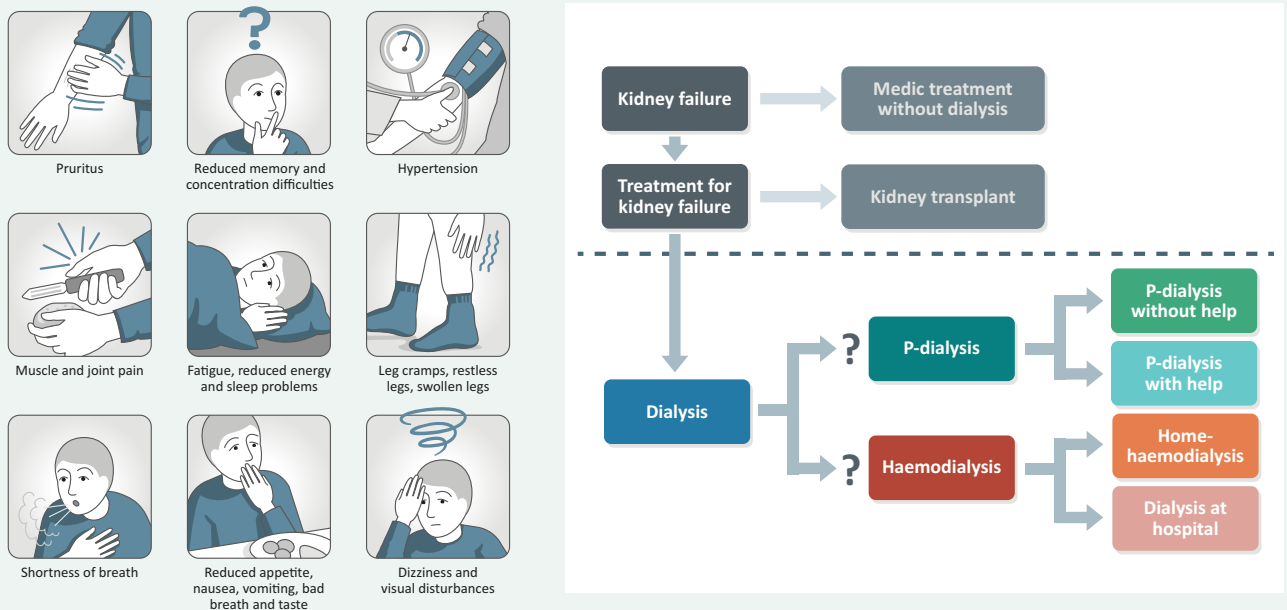


Figure 1. Screen shot from “Dialysis Choice” - decision map and overview of symptoms

Table 1. List of IPDAS criteria ¹⁰

Qualifying criteria to be defined as a patient decision aid

The patient decision aid:	
1. Describes the health condition or problem (treatment, procedure, or investigation) for which the index decision is required	5. Describes the negative features (harms, side effects, or disadvantages) of each option
2. Explicitly states the decision that needs to be considered (index decision)	6. Describes what it is like to experience the consequences of the options (e.g., physical, psychological, social) or includes an explicit values clarification exercise
3. Describes the options available for the index decision	
4. Describes the positive features (benefits or advantages) of each option	

Criteria to minimise risk of bias in the patient decision aid

The patient decision aid:	The patient decision aid for screening or diagnostic testing:
1. Shows the negative and positive features of options with equal detail (e.g., using similar fonts, sequence, presentation of statistical information)	7. Describes what the test is designed to measure
2. Provides citations to the evidence selected (or provides them in an associated document)	8. Describes the next steps typically taken if the test detects the condition or problem
3. Provides a production or publication date	9. Describes the next steps if the condition or problem is not detected
4. Provides information about the update policy (or provides this information in an associated document)	10. Has information about the consequences of detecting the condition or disease that would never have caused problems if screening had not been done (lead time bias)
5. Provides information about the levels of uncertainty around event or outcome probabilities (e.g., by giving a range or by using phrases such as “our best estimate is ...”)	
6. Provides information about the funding source used for development (or provides this in an associated document)	

Criteria indicating the quality of the patient decision aid

The patient decision aid:	10. Provides a step-by-step way to make a decision	20. Includes authors’/developers’ credentials or qualifications
1. Describes the natural course of the health condition or problem if no action is taken (when appropriate)	11. Includes tools like worksheets or lists of questions to use when discussing options with a practitioner	22. Reports readability levels (using one or more of the available scales, or provides this information in an associated document)
2. Makes it possible to compare the positive and negative features of the available options	12. Reports the development process included a needs assessment with clients or patients	22. Has evidence that it improves the match between the preferences of the informed patient and the option that is chosen
3. Provides information about outcome probabilities associated with the options (i.e., the likely consequences of decisions)	13. Reports the development process included a needs assessment with health professionals	23. Has evidence that it helps patients improve their knowledge about options’ features
4. Specifies the defined group (reference class) of patients for whom the outcome probabilities apply	14. Reports the development process included a review by clients/patients not involved in producing the decision support intervention	Patient decision aids for screening or diagnostic testing:
5. Specifies the event rates for the outcome probabilities	15. Reports the development process included a review by professionals not involved in producing the decision support intervention	24. Includes information about the chances of having a true-positive test result
6. Allows the user to compare outcome probabilities across options using the same time period (when feasible)	16. Was field tested with patients who were facing the decision	25. Includes information about the chances of having a true-negative test result
7. Allows the user to compare outcome probabilities across options using the same denominator (when feasible)	17. Was field tested with practitioners who counsel patients who face the decision	26. Includes information about the chances of having a false-positive test result
8. Provides more than one way of viewing the probabilities (e.g., words, numbers, and diagrams)	18. Describes how research evidence was selected or synthesised (or provides this information in an associated document)	27. Includes information about the chances of having a false-negative test result
9. Asks patients to think about which positive and negative features of the options matter most to them (implicitly or explicitly)	19. Describes the quality of the research evidence used (or provides this information in an associated document)	28. Describes the chances the disease is detected with and without the use of the test

Decision Aids.⁷ The aid is intended to be used by patients with chronic kidney disease to help them choose dialysis options during shared decision making meetings with a dialysis coordinator and with their family at home. The dialysis coordinator is a nurse who is specially trained to deliver the intervention that requires tailoring the decision support and using three different communication skills: mirroring, active listening, and value-clarifying. Dialysis choice includes a decision map and an overview of symptoms to help understand why a choice is being made and which options are available (e.g. peritoneal dialysis versus haemodialysis at home or in the hospital). The goal of the aid is to provide insight into and to foster discussion of the advantages and disadvantages of each option. Further, the aid includes a “values clarification” exercise that asks patients to rate the importance of different option features according to a five-point scale. During meetings with the patient, the dialysis coordinator uses the patient’s responses from the decision aid to tailor the support to each of the patient’s needs, expectations, and values.

Dialysis Choice was developed in Aarhus, Denmark, and evaluated in four Danish hospitals. It has since been implemented in three other Danish hospitals.¹³⁻¹⁵ In evaluations, Dialysis choice increased patient involvement in decision making and led to choices that reflected patients’ values for outcomes of options.^{14,15} Using this aid, patients more often chose a home-based than a hospital-based treatment,¹³ and those receiving home-based treatments became more involved in their treatment and healthcare over time.¹⁶ Dialysis choice, along with meetings with the dialysis coordinators, were the two active mechanisms contributing to the improved decision making.¹⁴

The “Dialysis Choice” patient decision aid is publicly and freely available in Danish, English, and Arabic in the A to Z inventory at Ottawa Hospital Research Institute.⁷ Based on the IPDAS criteria, “Dialysis Choice” met all defining criteria, all but one criterion to minimise risk of bias (it does not provide references to the scientific evidence used), and most of the quality criteria. In fact, the patients involved in the development process had asked that the sources

of evidence not be included in the decision aid.

After using the patient decision aid, one patient stated:

*“But when you sit there naïve and don’t know anything, it [the decision aid] can help a lot. Also that you get more information about it [the decision].”*¹⁴

After starting home haemodialysis, another patient stated:

*“Well, they [the decision coach meetings] have contributed to making me realise what I’ve started. There haven’t been any big surprises. Nothing has shocked me. I would even say that the first dialysis session was exciting in some ways, because knowing that I have come this far and now we had to cross to the other side of the road.”*¹⁶

During meetings with the patient, the dialysis coordinator uses the patient’s responses from the decision aid to tailor the support to each patient’s needs, expectations, and values.

Rapid development of a patient decision aid to help nursing home residents considering a move to their family’s home during the COVID-19 pandemic.

In Spring 2020, at the beginning of the COVID-19 pandemic, several outbreaks occurred in

Canadian nursing homes. As a result, many families wondered whether they should reduce the older adults’ risk of contracting COVID-19 by moving them into their home. However, this decision had several potential benefits and harms that needed to be weighed. A decision aid to support families in making this decision was rapidly developed by a team of experienced patient decision aid developers and healthcare professionals experienced in caring for older adults in Ottawa, Canada.¹⁷ The aid was based on the well-tested Ottawa Decision Aid Template and the Ottawa Personal Decision Guide¹⁸ and developed based on a recent umbrella systematic review, which indicated that patient outcomes did not differ when older adults lived in a private home or nursing home as long as their personal care needs were met.¹⁹ Value statements in the decision aid were developed based on public responses to media releases in the Canadian news focusing on COVID-19 outbreaks in nursing homes. The patient decision aid was developed within two weeks and was endorsed by the National Institute on Ageing of Canada. It was then widely disseminated through Ottawa

Hospital Research Institute’s the A to Z Inventory of Patient Decision Aids and through traditional and social media. It has since been downloaded more than 25,000 times.¹⁹

User feedback of the decision aid has been positive. For example, one user said:

*“Thank you to you and your team for putting out resources that will allow families to make informed decisions about their loved ones during this pandemic. My wife, 51, lives with dementia at a long-term care home. I found your document to be most helpful.”*¹⁹

How to involve patients and healthcare professionals in the development of patient decision aids

IPDAS recommend that patients and healthcare professionals participate in the various stages of developing a patient decision aid.²¹ This can be done, for example, by asking patients and healthcare professionals what they need to prepare to discuss a decision, reviewing the decision aid by experts (e.g., healthcare professionals, patients) who were not involved in its development, and field testing the decision aid with patients facing the decision and healthcare professionals who counsel patients on the options.⁸ More recently, healthcare professionals and patients participate as partners on the research team during the design of patient decision aids.²⁰ A recent survey of 98 researchers who had used a randomised trial design to evaluate 108 patient decision aids found that co-design by healthcare professionals and patients is important for ensuring that decision aids intended for patients and healthcare professionals fits within clinical practice.²¹

According to a 2021 IPDAS update,²² development of patient aids should be an iterative process comprising three different phases:

- Understanding the decision making needs of the patients and the healthcare professionals through interviews, surveys, observations, literature reviews, etc.
- Developing the patient decision aid in a collaboration between patients and healthcare professionals, e.g. through multidisciplinary workshops
- Assessing the interactions and experiences of patients and healthcare professionals when using the patient decision aid

Patient and public involvement in research can contribute to development and evaluation of patient decision aids.²³ In the Dialysis Choice

example, both patients and healthcare professionals were involved throughout the research.²⁴ One patient was particularly proud of the aid and wanted all Danish hospitals to use it.²⁴ For the COVID-19 location of care example, it was developed so rapidly that only healthcare professionals were included in the small development team. Authors acknowledged the limitation of not involving patients.¹⁷

How to report research on patient decision aids

Reporting on the characteristics of patient decision aids is currently suboptimal. A review of 17 randomised controlled trials revealed that only 59% of authors reported all IPDAS qualifying criteria. This made it difficult for readers to determine whether the tested intervention was, in fact, a patient decision aid, and few trials described the patient decision aid adequately to

determine if the IPDAS criteria for minimising the risk of bias were addressed.²⁵ Further, the IPDAS update on patient decision aid development²² does not include an adequate description of the development process, although authors can provide additional details in appendices or other supporting documents.

In 2018, the IPDAS collaboration developed SUNDAE (Standards for Universal reporting of patient Decision Aid Evaluation Studies) for reporting studies evaluating patient decision aids. Two related papers were published, one describing the reporting standards and the guideline development process²⁶ and the other elaborating on the standards with examples demonstrating their use.²⁷ The SUNDAE guideline is included in the EQUATOR Network of reporting guidelines, and journals are encouraged to have their authors follow it and acknowledge its use.²⁸ A search in Google Scholar on May 20, 2021,

found that the first paper has been cited 59 times and the second paper 9 times in the first 3 years since their publication. Some journals also require the SUNDAE checklist to be attached as supplementary material. Some studies have supported that the SUNDAE guideline helps ensure adequate reporting of patient decision aids.¹⁵

Perspectives on using good-quality patient decision aids in healthcare

High-quality evidence indicates that patient decision aids are effective interventions that lack associated harm.⁵ However, getting them incorporated into routine clinical practice can be challenging. In the survey of 98 authors of 108 patient decision aid trials, 28% of the authors reported that the patient decision aid was implemented after the trial.²¹ Barriers to uptake in the clinic included outdated decision aids

Table 2. Strategies for implementing patient decision aids^{29,32}

Focus area	Strategies for implementation
Intervention characteristics	<ul style="list-style-type: none"> ● Keep patient decision aids as simple as possible and use plain language ● Establish processes for their use in clinical practice
Clinical practice setting	<ul style="list-style-type: none"> ● If patients have a strong emotional response to a new diagnosis or condition, help them come to terms with the diagnosis so that they will be better able to process the information in a patient decision aid ● To identify suitable patient decision aids, health professionals need to assess the patient’s decision-making needs ● Help the whole team understand the value of patient decision aids and their roles in decision processes (senior leadership, administrative staff, healthcare professionals) ● The patient decision aids need to be provided to the patients and to be discussed by both patients and healthcare professionals ● Provide continuing education for staff focused on patient decision aids and how to support patients in decision making ● Ensure that senior leadership supports and encourages the use of patient decision aids
Characteristics of individuals	<ul style="list-style-type: none"> ● Health professionals who are aware, trained, and motivated to use patient decision aids and understand their intended use ● Engage health professionals in selecting the patient decision aid and establishing the best processes for its use ● Have health professionals invite and encourage patients to use decision aids ● Be aware of potential for significant power imbalances between patients and health care professionals
Process	<ul style="list-style-type: none"> ● Embed patient decision aids early in the process when health professionals initially communicate options to patients ● Establish delivery of patient decision aids to all eligible patients ● Use patient decision aids within a “learning health system” whereby measured patient decision aid outcomes are monitored and used to inform care as well as quality improvement initiatives



coupled with a lack of funding for updates, reluctance of healthcare professionals to use the aid, and lack of infrastructure support. A recent rapid realist review of 23 implementation studies found that patient decision aids become successfully implemented into clinical practice when their content and application was done in collaboration with patients and healthcare professionals; the whole team was trained; patients were prepared and prompted to engage in decision making; support from management was ensured; and measures to monitor quality of decision making were used.²⁹ Strategies for implementing patient decision aids are summarised in Table 2.

Use of patient decision aids is supported by several healthcare systems. For example, “Patient Experience in the National Health Service in the UK” recommends the use of high-quality patient decision aids.³⁰ Also, the US Center for Medicare and Medicaid Services provides reimbursement when a patient decision aid is used for the first lung cancer screening by low-dose computed tomography.³¹

Conclusion

Guidelines are available to help develop high-quality patient decision aids, and evidence indicates that they are effective at improving health decision making. In addition, the SUNDAE reporting guidelines are available for studies describing patient decisions aids, and an international repository of publicly available quality-rated patient decision aids is available through Ottawa Hospital Research Institute’s A to Z Inventory of Patient Decision Aids.

Further, several countries already have health policies recommending the use of patient decision aids in healthcare services. The next priority is to make their use part of routine clinical practice.

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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EUPATI: Patient engagement through education as an important contributor to shared decision making

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Abstract

Building knowledge and capacity for patients and their advocates about the “systems” of healthcare is empowering for patients. The European Patients’ Academy (EUPATI) was established across Europe in 2012 to provide education and training to patients and their advocates. Initiatives like EUPATI have broken new ground in terms of patients’ education and learning opportunities. Taking their knowledge back into decision making bodies like the UK’s National Institute for Health and Care Excellence (NICE) can lead to a greater focus on the issues that matter most to patients. That focus on the outcomes and issues of concern to patients give those of us working in this field the opportunity to take population-level recommendations as the basis for individualised decisions, shared between patient and clinician.

EUPATI

The European Patients’ Academy (EUPATI)¹ was established across Europe in 2012 to provide education and training to patients and their advocates. The purpose of the initiative (part of the Innovative Medicines Initiative²) was to increase patients’ understanding of and contributions to medicines research and development, and to improve the availability of objective, reliable, and patient-friendly information for the public. Its aim was also to build capacity in Europe and beyond to accelerate patient engagement in all aspects of the development of medicines.

As a founding member of EUPATI’s multi-stakeholder consortium (which brings together patients, pharmaceutical industry, academia, non-profit organisations, regulators, and health technology assessment [HTA] bodies), it has been an extraordinary privilege for me to see the successful graduation of more than 200 EUPATI scholars over the years, knowing that the cascade of their knowledge and experience is being felt worldwide.

What does EUPATI offer its students?

The EUPATI syllabus covers several modules under the following broad headings: introduction to medicines R&D, non-clinical development, clinical development, regulatory affairs, and health technology assessment. Further details about the modules can be found in their current brochure.³ EUPATI’s website contains much information which is free to use, including the toolkits which form essential content for its formal students. People have the option to use this content as a guest but to become a registered EUPATI fellow one needs to become a “formal learner”. The content for formal learners remains free to use, but there is a small (8 Euro) charge to cover assessment costs for each module. Anyone with an interest can register to become a formal learner.

The EUPATI course has moved predominantly online to the platform called the “Open Classroom”⁴ with some face-to-face and streamed sessions, all of which comprise a mix of taught and interactive modules, with opportunities for discussions and practical exercises (Figure 1). EUPATI offers most of the course on a flexible and “on-demand model”, allowing the students to study around their other commitments.

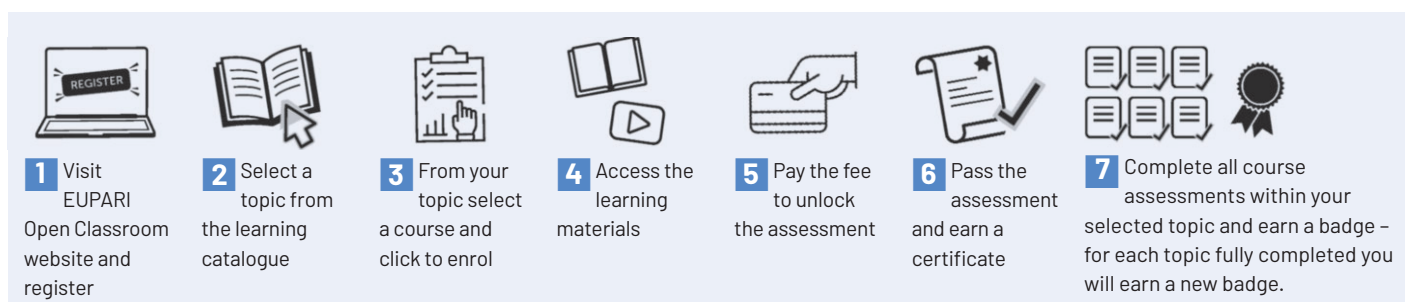


Figure 1. How does EUPATI Open Classroom work?



Health technology assessment

One of the key parts of the EUPATI training is the module on HTA⁵ and the role that patients, carers, and the public can play in shaping these evaluations. As explained in this module, the UK's National Institute for Health and Care Excellence (NICE) has responsibility for delivering HTA recommendations for the health service in England.⁶ NICE's Public Involvement Programme supports the involvement of patients and the public in this work⁷ that is integral to how NICE operates across all its programmes.

The recommendations that NICE produces as part of its HTA programmes are designed to support the health service in England by identifying the technologies that deliver effective treatments for patients in terms of improving people's outcomes. The NICE recommendations also include interventions that deliver cost-effectiveness (or, in essence, value for money) for the UK healthcare system.

Evidence-based decisions for broad populations

The EUPATI initiative was established as a means to educate patients on the life cycle of

medicines, to give patients an understanding of the process of taking a medicine to market, and to understand the broad mechanisms by which patients can be involved in all stages of medicines development. Part of this process is the identification, analysis, and appraisal of the best available evidence – including evidence generated about and by patients.

However, one of the limitations of evidence-based medicine – and its application in the HTA process in particular (exemplified by NICE) – is that the recommendations developed are based on standardised care for broad populations of patients. Individual decision making (and by association, key aspects of personalised medicine), and the science of how we make decisions about our care, have not routinely been considered as part of this approach. Some new initiatives at NICE are paving the way for formally translating these population-level decisions into mechanisms for individual patients to make individual decisions about their care.

Part of this process is the identification, analysis, and appraisal of the best available evidence – including evidence generated about and by patients.

These have included to date the development of patient decision aids for a number of topics,⁸ and the identification of “preference-sensitive” decisions during the development of recommendations. These decisions may be preference-sensitive due to a lack of evidence, the uncertainty of evidence, or – most importantly – where a person's individual circumstances, experiences, values, and preferences would lead them to make individual choices.

Shared decision making (SDM)

The concept of patients and clinicians working together to jointly decide on the best course of action for that particular patient is not new. Indeed, it is at the heart of what we would all hope for from a successful consultation with a health professional. There are circumstances when all of us would like others to act in our best interests, and we hope that they use the best available evidence to make decisions on our

behalf. However, in most clinician/patient interactions and in many clinical circumstances, there are opportunities for a considered approach to the evidence where the treatment options can be weighed up and patients and clinicians can discuss, as equals, the best option for the individual in question.

We all have different attitudes to risk, and when presented with the same clinical options, we might make different choices to one another. It is important that we have access to standardised information about our treatment options so that we can reach a decision about what would best reflect our own values and preferences and be able to discuss these with our clinicians.

The value that patients' understanding and involvement brings to these processes, by identifying the issues that matter most to them and the questions they wish to pose to their clinicians, is unique and vital. NICE's longstanding involvement of patients in its guidance development, and latterly in its work around shared decision making, demonstrates time and again this added value.⁹

We know from a recent Cochrane review¹⁰ that tools to support these individual discussions and decisions (e.g. decision aids, patient decision aids, option grids) can make people more knowledgeable, better informed, and clearer about their values – and in all likelihood, they will have a more active role in decision making and more accurate risk perceptions.

These tools also support clinicians by providing easy access to standardised information that they can share with their patients in pursuit of a shared decision about treatment. Shared decision making is still not embedded in routine clinical practice, and Joseph-Williams et al¹¹ have articulated why this might be (e.g. assumptions that patients are not interested in making decisions, that there are not the tools to support it, not knowing how to measure it, etc.) and how the barriers to integration might be overcome.

We are hopeful that the work that NICE is currently developing in this field will also add to the tools that support a change in culture whereby shared decision making is not only a

We all have different attitudes to risk, and when presented with the same clinical options, we might make different choices to one another.

part of routine care but is also part of our approach to developing evidence-based guidance and HTA recommendations.

We have produced a set of guideline recommendations on good practice in shared decision making.¹²

Alongside this, we have collaborated with Keele University to develop an online learning package to support clinicians in delivering a shared decision making approach.¹³

We have published a quality framework for people who are decision aid users and developers, whether they are patients or clinicians.¹⁴ This piece of work was commissioned from NICE by NHS England.¹⁵

Finally, as part of NICE's five-year strategy,¹⁶ we will be developing mechanisms by which shared decision making can form an integral part of NICE's methodologies and processes.

Conclusion

Both the EUPATI initiative and the two decades of patient and public involvement at NICE have demonstrated the value of enhancing patients' understanding of the processes by which treatments and interventions make their way into health care systems. These processes have typically stopped short of including an analysis of the science of decision making and of the potential tension between recommendations intended to realise benefits at a population-level and the choices and potential benefits for the individual.

NICE is aiming to help resolve this tension by incorporating shared decision making into its methods and processes, providing a quality framework for decision aids, and continuing to support clinicians, patients, and the general public in participating in shared decision making. In this way, NICE hopes to draw together the need for population-level, evidence-based recommendations and the importance of individualised personalised decision making.

Disclaimers

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

Conflicts of interest

The author is employed by the National Institute for Health and Care Excellence. She is also part of the founding consortium for the European Patients Academy on Therapeutic Innovation.

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The regulatory-HTA decision-making interface: What the medical writer should know

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Abstract

For a new medicine to reach patients, it must achieve both regulatory marketing authorisation and reimbursement from the payer. Because regulators assess the benefits and risks of a medicine while the health technology assessment (HTA) bodies assess its value to the system, their informational needs differ. Two different but potentially aligned dossiers are therefore required: the regulatory dossier and the HTA submission dossier. The medical writer must be prepared to contribute to both. Herein we review the basic elements of the regulatory dossier, the

Global Value Dossier and the HTA submission dossier. For the medical writer, an important challenge is how to determine whether there can be alignment and synergies between regulatory data and HTA data to support the respective decision-making processes. Practical approaches to the construction of the submission documents are provided here. These approaches bring consistency to the documents, serve as a checklist for relevant information, and facilitate the review by the assessor.



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Aligning regulatory and HTA expectations

Bringing a new medicine to the market is dependent on two successful processes: achieving market authorisation from the regulatory agency and for single-payer countries, reimbursement from a payer. Because the healthcare environment is faced with growing pressures to control healthcare costs, payers need to make decisions on the reimbursement of medicines to maximise public health outcomes within limited health budgets. Consequently, an important stakeholder has emerged – the health technology assessment (HTA) body whose goal is to make recommendations on reimbursement on the basis of the value of a new therapy to both the patient population and the healthcare system. Consequently, drug developers seeking to deliver new medicines need to coordinate a development programme to generate evidence that meets the needs of both regulatory and HTA agencies.¹ Using a “piggyback” approach in which health-economic data are collected within an otherwise typical clinical trial, has been explored as one way to coordinate the efficient collection of information that will be useful for both the regulatory and HTA submission.²

Medicine regulators evaluate the quality, safety, and efficacy of products to ensure that the products they authorise meet local and, where applicable, regional, or international standards. Assessments of novel products are based on dossiers prepared and submitted by the pharmaceutical sponsors. To facilitate the presentation of regulatory information in a consistent manner, under the auspices of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the standardised presentation format designated the Common Technical Document (CTD), has been implemented. This approach has standardised the submission format and content, made the regulatory review process more efficient, and has led to harmonised electronic submissions that, in turn, have enabled the implementation of good submission and review practices. For pharmaceutical sponsors, it strives to reduce the need to reformat the information for submission to different regulatory authorities.

The CTD is organised into five modules. Module 1 is region specific, and Modules 2, 3, 4,

and 5 are intended to be common for all regions. Details of the format of the CTD are available here: <https://www.ich.org/page/ctd>. While it is not within the scope of this article to review the component elements of the CTD, the medical writer who is responsible for preparing regulatory submissions must be thoroughly familiar with the structure and format of the CTD. Consequently, the medical writer must be well informed about the components of the CTD and to be able to construct the various types of documents within the submission. These range from detailed clinical study reports to section summaries and more succinct overviews. ICH guidelines provide the details that ensure consistency and completeness of the submission. Consistency of structure underpins efficiency and addresses the clear presentation and availability of data to support quality, safety, and efficacy and the expectations of regulatory reviewers.

When the structural components of the CTD are addressed, the CTD is designed to provide the regulator with sufficient information to make

an informed decision of the balance between the clinical benefits of the product and its risks. If harms are to be expected, then the CTD defines ways to mitigate and control for these harms. While clinical data comparing the new product to another active comparator may form part of the submission, comparative efficacy is generally not a requirement for the evaluation of efficacy. Therefore, where ethically possible, placebo comparisons and the use of other novel comparator approaches may form the basis for the regulatory benefit-risk decision. Consistent with making decisions on specialised data sets that may not be able to address all the uncertainties regarding the benefits and harms of a product, is the importance of post-authorisation commitments and their reporting through periodic benefit-risk evaluation reports (PBRERs). Many medical writers focus their attention on these specialised reports.

The approaches that regulators take to making their benefit-risk decisions have a defined scope. The decisions do not typically address the comparative efficacy of the new product to an existing therapy nor do regulatory decisions consider the cost of the therapy or its pharmacoeconomic impact to a healthcare system. It is

therefore the role of the HTA body to address the “value” of the new medicine to the healthcare system.³ Is the efficacy of the product an improvement above existing standards of care? Does an improvement in the safety profile or dosing regimen contribute to adherence and better outcomes? Is the proposed cost of the product to the healthcare system worth these benefits? These are questions that HTA bodies must address, and it is the role of the medical writer to provide the substantive evidence required to support the HTA decision making process.

The medical writer has several tools at their disposal to address the concept of a product’s value. These include the Global Value Dossier and the HTA submission dossier. To establish, support, and convey a product’s value during the lifecycle of a product, companies will prepare a Global Value Dossier, which serves as a dynamic value roadmap for internal use and then as the core information resource for HTA submissions.⁴

As with the regulatory dossier for the regulator, the HTA submission dossier provides information that will help the HTA body decide about the relative value of a new therapy. HTA bodies seek information through a dossier of pharmacoeconomic information to make a value recommendation to a payer. Unlike a regulatory dossier, the HTA submission dossier may address relative efficacy (the extent to which an intervention does more good than harm, under ideal circumstances such as a clinical trial, compared with one or more alternative interventions) and relative effectiveness (the extent to which an intervention does more good than harm compared with one or more alternative interventions for achieving the desired results when provided under the usual real-world circumstances of healthcare practice).⁵ Because the local affiliate often has the best knowledge of the specific country’s health economic issues, the local affiliate will use the Global Value Dossier as the basis for their HTA submission, with adaptations to meet the local medical, pharmacoeconomic, and value contexts.

In the past, however, the content of the HTA submission dossier has been inconsistent and has not always provided the substantive data in a clear and well-organised manner. Therefore, through its recent evolution, the HTA submission dossier has benefited from the development of a generic approach to the communication of the observations, similar to the way that the CTD

The medical writer has several tools at their disposal to address the concept of a product’s value.

has evolved. The pharmaceutical sponsor can now more easily present their observations in a cogent, well-organised manner in order to support a local HTA submission. And as the database of experience with a product continues growing, this approach also encourages the dynamic refinement of the comprehensive Global Value Dossier. While the medical writer may be the primary author of an HTA submission dossier, they may collaborate with a pharmacoeconomist in this activity.

Having the information presented in a consistent manner has several advantages: it serves as a checklist for the sponsor to identify the kinds of information that the HTA body will need to support its scientific assessment of the value of a therapy; it allows for the HTA body to conduct section-to-section comparisons across dossiers; and it facilitates conversations between the HTA body and sponsor by being able to point to easily accessed details.

A clear value message presented by the sponsor in the local HTA submission may also accelerate the HTA assessment process. Timely recommendations by the HTA bodies for drug reimbursement by the relevant payers are critical to ensure that patient access to medicines of therapeutic value is not delayed. As part of an ongoing study to monitor regulatory and HTA performance, Cai et al.⁶ assessed data on new active substances appraised between 2015 and 2019 by eight HTA bodies. Of the studied HTA bodies, Germany had the highest proportion of products recommended within one year of regulatory approval (92% in 2019). Australia had the shortest median time between regulatory approval and HTA recommendation (24 days) in 2015–2019, followed by Germany (132 days). The authors analysed new active substance products rolled out to seven jurisdictions and identified 37 products that received a recommendation by all HTA agencies during the period of 2015–2019. Germany provided the highest number of recommendations as the first country of appraisal (30%), followed by Australia (24%). This variability reflects the divergences of the organization, processes, and methodology among HTA agencies, and calls for development

of standards for best practice in HTA as well as the refinement of practical HTA tools.

Several approaches have evolved for structuring an HTA submission dossier. One approach is to use the PICO (Patient-Intervention-Comparator-Outcome) strategy, which helps organise thoughts and data.⁷ PICO is not widely used but can be considered a tool to organise thoughts.

For each HTA body, their defined value dossier submission template will be different; this is because each has been designed to meet the need of their own review process. PICO and related elements remain key to the dossier. Therefore, using a template to present data in an HTA submission dossier is as helpful as using the CTD structure to present regulatory information. The challenges faced by the medical writer are the divergences across the templates and lack of standard

framework. One example of a template for the presentation of HTA data has been developed by the National Institute for Health and Care Excellence (NICE) and can be found via this link: <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/company-evidence-submission-template-apr-17.docx>.

Another important approach that has evolved to address this issue is referred to as the Core Model (Figure 1). The European Network for Health Technology Assessment (EUnetHTA) provided details of how this model can be used by an HTA body to summarize the evaluation of a value dossier. The medical writer should familiarise themselves with the various ways that the Core Model can be used so that they can construct a value dossier that is consistent with the needs of the model.

At the base of the approach is the HTA Core Model for the production of core HTA assessments. An outcome of the EUnetHTA Joint Action on HTA (2012–2015), the HTA Core Model v 3.0 was developed as a component of Work Package 8 – Maintenance of HTA Core Model[®] infrastructure to support shared production and sharing of HTA information (see: <https://eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf>). EUnetHTA notes that the main aim of the HTA

Core Model is to enable international collaboration in producing HTA information and efficient sharing of the results so that redundant overlapping work in different countries and regions can be avoided. Normally, an HTA assessment contains a vast amount of information. The content, focus, quality, and reporting of these observations vary significantly; this makes finding and transferring the information into local contexts difficult. The HTA Core Model addresses these problems. The model defines the content elements to be considered in an assessment and enables standardised reporting, consequently providing a common framework for the production of the assessment.

The model describes 9 key domains:

- Health problem and current use of technology (CUR)
- Description and technical characteristics of technology (TEC)
- Safety (SAF)
- Clinical effectiveness (EFF)
- Costs and economic evaluation (ECO)
- Ethical analysis (ETH)
- Organisational aspects (ORG)
- Patients and Social aspects (SOC)
- Legal aspects (LEG).

Each domain is described in detail in the model. The domains of the Core Model address the range of elements that inform value assessments of HTA. Domains 1 to 4 are of a more general nature, while domains 5 to 9 are more jurisdiction-specific. The HTA Core Model, apart from standardising reporting and helping to avoid overlap, addresses the needs of individual countries' different requirements and different local conditions; therefore, the medical writer will have a meaningful framework to construct the Global Value Dossier from which one can produce the submission dossier, which can support the local HTA review.

Through the activities of the Joint Action on HTA 2012–2015 Work Package WP5, EUnetHTA developed in 2015 the HTA Core Model for the production of Rapid Relative Effectiveness Assessments (also called the Model for Rapid REA, version 4.2). The aims of the Model for Rapid REA are similar to those of the Core Model: to improve the applicability of HTA information in other (e.g. national or regional) HTA projects; to enable actual collaboration between HTA agencies by providing a common

For each HTA body, their defined value dossier submission template will be different; this is because each has been designed to meet the need of their own review process.

framework for the production of rapid REA; and to avoid duplication of work. Being derived from the HTA Core Model, the Model for Rapid REA provides an overview for producers of rapid REAs on the basic steps involved and on important generic research questions that should be considered in an HTA assessment. Rapid REAs contain an analysis of the product in comparison with one or more relevant alternative interventions, but the Rapid REA is limited to a subset of domains and performed within a limited timeframe (Figure 2). Item 5 is specific to a particular jurisdictional submission.

The Model for Rapid REA covers generic research questions for pharmaceuticals, diagnostics, medical, and surgical interventions, and screening technologies. For a detailed description of the domains, the guidance concerning assessments of specific types of technologies and other research questions to be considered within a rapid REA, is available at https://eunethta.eu/wp-content/uploads/2018/06/HTACoreModel_ForRapidREAs4.2-3.pdf.

It is important to note that the Core Model is helpful as a conceptual framework to help construct the evidence that will support an HTA submission but is not currently used by most medical writers unless they are preparing a submission for the EUnetHTA rapid assessment. However, a joint review by multiple HTAs may eventually become a norm in the EU, so it will gain importance at some point in future. (See https://eunethta.eu/wp-content/uploads/2018/01/roche_pharma_report_on_the_hta_core_model_december2014_0.pdf).

An information source of increasing significance in informing HTA decisions is the European Public Assessment Report (EPAR) created by the European Medicines Agency (EMA) for each newly approved medicine. While it has long been recognised that HTA bodies often are limited in the way that they can integrate data that support a regulatory decision into their value models (e.g. phase 2 data that support the safety and efficacy of a product may not be sufficiently robust to predict a long-term benefit and therefore may have limited applicability in determining the pharmacoeconomic value), it has also been recognised that the EPAR can serve as an important source of validated information to help inform the HTA assessment.⁸ Collaborations between the EMA and HTA bodies are resulting in the development of EPARs that can be used more effectively by

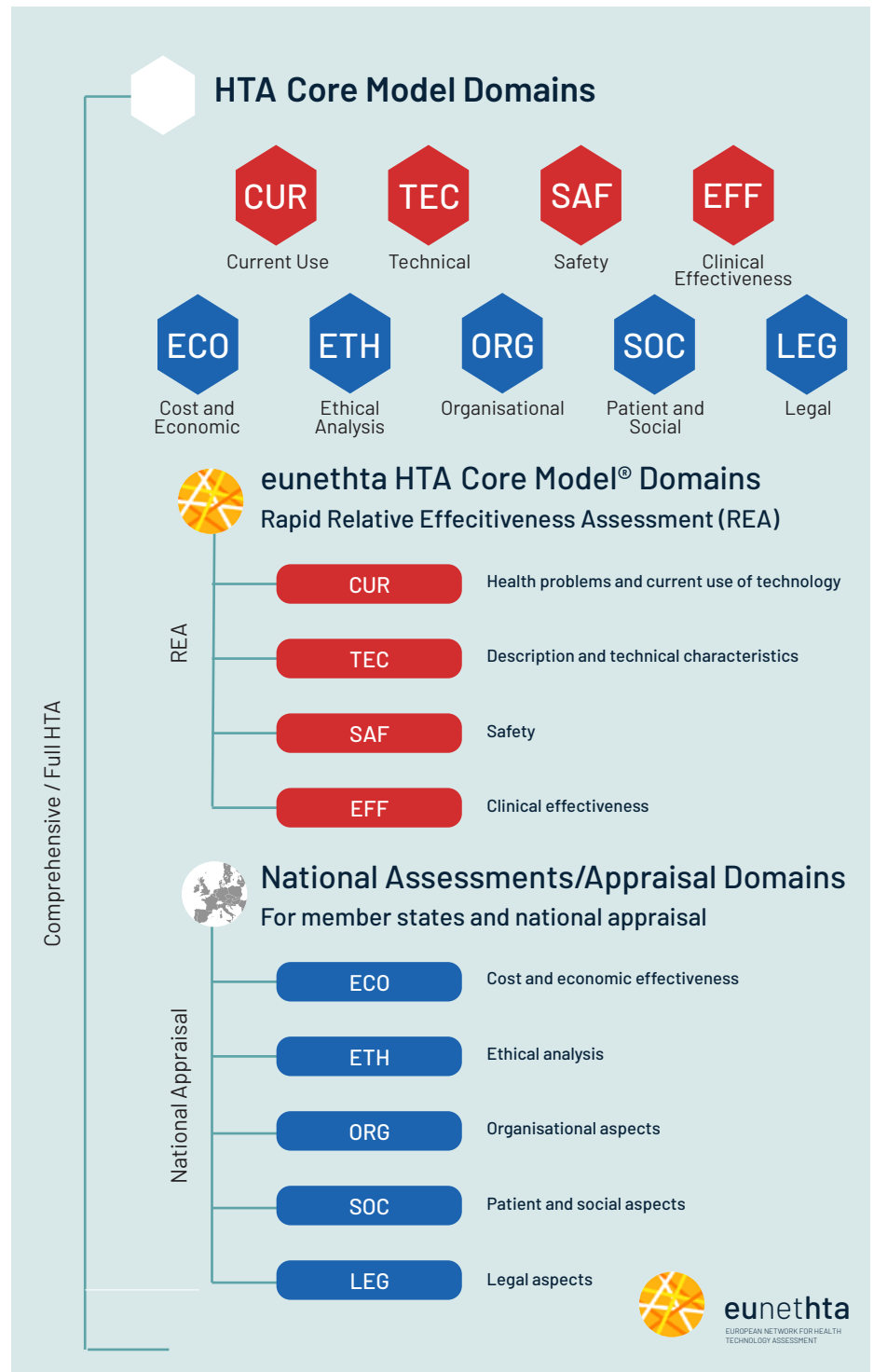


Figure 1. The domains of the EUnetHTA Core Model

Source: <https://eunethta.eu/hta-core-model/>



Photo: Unsplash / LPW

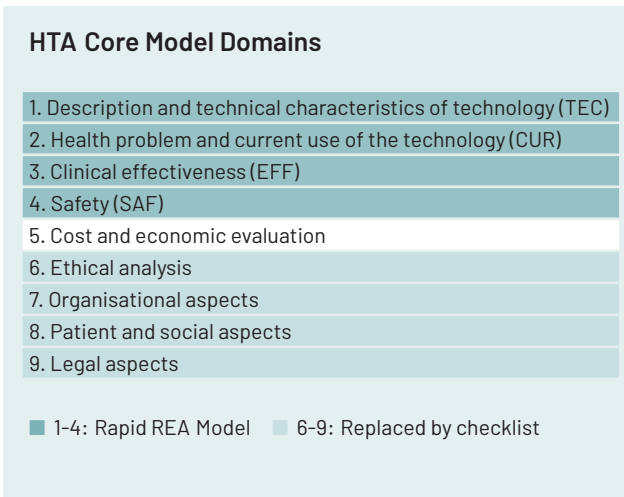


Figure 2. How the Domains of the HTA Core Model® and of the HTA Core Model for Rapid Relative Effectiveness Assessments overlap

Source: <https://eunetha.eu/wp-content/uploads/2018/06/HTACoreModel-ForRapidREAs4.2-3.pdf>

HTA bodies in their decision-making process. Therefore, the medical writer should familiarise themselves with a product’s EPAR as they prepare the value dossier.

A new challenge has emerged with the preponderance of innovative products that are receiving regulatory authorisation where there is an unmet medical need and therefore, few therapeutic options. Using facilitated regulatory pathways (FRPs) such as the breakthrough therapy designation, priority and accelerated reviews and conditional marketing authorisations, important new therapeutic options with good signals of clinical efficacy are being approved in record times. However, the paucity of long-term data – and therefore the reliance on surrogate endpoints

for the regulatory decision – make formulating a value recommendation complicated. Most models used by HTA bodies are limited in the manner that these short-term data are integrated to establish value. Consequently, HTA bodies and payers are investigating novel approaches to reimbursement that reassess the value of a therapy as data are accumulated, including concepts such as coverage with evidence development, cost sharing, and price-volume agreements.^{9,10}

For the medical writer, an important challenge is how to determine whether there can be alignment and synergies between regulatory data and HTA data to support the respective decision-making processes.¹ As HTA bodies and regulators more closely align

For the medical writer, an important challenge is how to determine whether there can be alignment and synergies between regulatory data and HTA data to support the respective decision-making processes.

their expectation and goals, the process of developing aligned evidentiary requirements will evolve to facilitate the decision-making process.¹¹ As the successful work of EUNetHTA comes to an end in 2021, we are left with questions about what will the post-EUNetHTA landscape look like and what will the medical writer need to prepare for? Over the decades, medical writers have been characterised by their flexibility and adaptability. Now more than ever, the medical writer must convince their colleagues to adopt a flexible and adaptive stance in the context of evolving predictive and adaptive models of research and development. As the need to align regulatory and HTA decisions grows, so too will the new skills of the medical writer.

Conflicts of interest

The authors cite no conflicts of interest.

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Communicating the findings of health technology assessments: Considering uncertainty

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Abstract

Uncertainty is an unavoidable problem when analysing health technology assessment results, which can make decision making difficult. Whilst we have ways of presenting uncertainty for individual outcomes in a systematic review, we do not have a succinct and uncomplicated way to demonstrate the various sources of uncertainty across the clinical, applicability, and economic aspects of an HTA. This article discusses several sources of uncertainty that are present in health technology assessments and highlights certain challenges associated with reporting them. Transparency is key to ensuring that health technology assessments have the greatest utility for decision makers and that trustworthiness in the process is maximised.

Ever since the beginning of clinical research and more recently, health technology assessments (HTA), researchers have been dealing with uncertainty. The Oxford Dictionary defines uncertainty as “The state of not being definitely known or perfectly clear; doubtfulness or vagueness.” In health, uncertainty may be due to ignorance or failure, and acknowledging uncertainty can be uncomfortable for clinicians.² Also, medical research is imperfect, many factors, both known and unknown, and modifiable and fixable, affect the results and impact on how much we can trust them. These uncertainties are not desirable characteristics to associate with big decisions¹ and may sound frightening in relation to health decision making.

Understanding the quality of the research, the limitations to its conduct, and its real world applicability is paramount to good decision making for both patients, carers and for policy and reimbursement decision makers. It is this understanding, interpretation, and application that elevates an HTA beyond its components of systematic review and economic analysis.

The work of HTA can be highly technical and complex, with many factors that contribute to the findings in both the clinical and economic assessments. It is a key task of health technology analysts to be able to identify the “important” results and communicate these effectively. End HTA users are often time-poor and are unlikely to read the complete technical documents associated with a full HTA that includes a comprehensive systematic review and full economic modelling. In Australia, for example, the committee charged with making recommendations for public funding on medical devices and tests (Medical Services Advisory Committee, MSAC) consider as many as twenty new devices at each triannual meeting. The equivalent committee for assessing drugs (Pharmaceutical Benefits Advisory Committee, PBAC)

may consider the same number of new drug listings as well as applications for changes to current listings. As producers of HTAs, we understand this and are under increasing pressure to condense our findings into the most succinct form possible, making sure that the important issues are highlighted. Whilst this is mostly achievable when communicating *results*, it is more difficult when it comes to communicating *uncertainty* around those results. This paper will discuss some of the uncertainties that may be present in the clinical and economic components of HTAs and will highlight some of the ways that these uncertainties can be addressed when presenting an HTA.

Sources of uncertainty

Within the clinical assessment section of an HTA (i.e. the assessment of safety, efficacy, and effectiveness), uncertainty can arise from the type and quality of available evidence. We know that the randomised controlled trial (RCT) is the gold standard of interventional research (such as new medicines or devices). But whilst there are many thousands of RCTs produced every year, there is not always RCT evidence available for the intervention (or population, or comparator) of interest. With new technologies, the evidence base is sometimes immature, with too few large or rigorous studies conducted to ascertain efficacy and safety with any certainty. In other cases, there may be a large body of evidence, but

of studies lower on the hierarchy of study design,³ such as was found in a Canadian HTA of implants for hearing loss.⁴ In this HTA, 20 systematic reviews were included, but the vast majority of the primary evidence was from small case series, in which patients were studied before and after the intervention. These types of studies are not as reliable as RCTs, giving lower confidence in the evidence overall. Other evidence bases may demonstrate

heterogeneity in uncertainty across distinct parts of the evidence base such as particular outcomes, population sub-groups, or follow-up periods. This can be evident with safety outcomes in particular, where RCTs are often underpowered to detect rare but important adverse events. This was seen in a systematic review of safety outcomes for the human papillomavirus vaccine undertaken for the World Health Organization, where despite the many well-designed and large size RCTs included, rare adverse events were generally not identified.⁵ If other information about safety is not available, such as from large observational studies or studies including real world evidence (such as administrative databases from hospitals or

Uncertainty is an unavoidable problem when analysing health technology assessment results, which can make decision making difficult.



primary care), this can leave a gap in the knowledge about key clinical outcomes.

Of course, an RCT is not a guarantee for quality. RCTs are subject to methodological bias, which results in uncertainties in the findings. In fact, well-designed and executed observational studies can be more trustworthy than poorly designed and executed RCTs. It is very common for the evidence base in an HTA to contain more than one study type, and for the quality across the outcomes – and the studies – to be mixed. The tasks of understanding the sources of uncertainty and interpreting their importance across the body of evidence in these types of HTA is challenging.

Understanding uncertainty can be compounded within economic analyses undertaken for HTA as the multiple inputs into economic models can have varying levels of uncertainty.

The incremental cost effectiveness ratio (ICER), a measure of the extra cost associated with a unit of extra benefit, commonly a quality-adjusted life-year, is now the preferred metric for decision making in many jurisdictions, but this approach often relies on a number of assumptions to estimate the health gain and the utilities associated with various health states, and to extrapolate over time. Uncertainty in economic models is typically explored through scenario and sensitivity analyses, for example where the smallest and largest plausible estimates for model inputs are tested to see the impact on the results.⁶ The uncertainty around various aspects of these models can be described in different ways, but it is safe to say that these highly complex and extremely technical analyses can be difficult for non-economists to grasp. Again, we rely on the analyst to help the reader understand where the

uncertainty lies and how it impacts the result.

Uncertainty can also arise through applicability. Applicability refers to the ability of a new technology to fit into the existing landscape of clinical practice, infrastructure, and policies. To show applicability, the evidence base requires assessing the technology and intervention within the population and setting appropriate for its intended use. This may include considering clinical and demographic factors in the study the populations, including the disease spectrum, and technology delivery. Applicability uncertainty may be extrapolated to more pragmatic issues: Does the technology require specific workforce training or accreditation? What equipment is required, and can it be housed within existing infrastructure? Can all people who will be eligible to receive the technology access it? Is there likely to be “leakage”, i.e. uptake of the technology by

Table 1. Issues to consider when reporting results of HTA

Concept	Description
Clinically important effects	Distinguish between clinically important and statistically significant effects; statistical uncertainty can be unrelated to the intervention, whereas clinically important effects are more likely to be related to the intervention
Patient-relevant outcomes	Prioritise the reporting of findings in patient-relevant outcomes when considering safety and effectiveness, and prioritise direct outcomes over surrogate outcomes
Compounding uncertainty in economic models	Consider that uncertainty in the clinical (and other) evidence used in any economic modelling will also have an impact on the results and could be multiplied when several uncertain inputs are used. If appropriate, best- and worst-case scenarios can be helpful as they are easily understood.
Case of no or insufficient evidence	Be explicit about where there is no evidence; where there is insufficient evidence (and why); and, where there is heterogeneity across the evidence base, e.g. some outcomes are uncertain and some are more certain. This helps decision-makers understand where the limitations are.
Recipients	Consider the differences between the needs of policy makers or funders (for whom the HTA is designed) and the needs of consumers, especially with regard to language and use of statistics.
Visual representations	Where appropriate, results can be presented visually. There is no standard way of visually representing uncertainty, but some ideas include a traffic light system or a thermometer-style measure (cold=uncertain, warm=more certain)

people it is not intended for? Some of the time, assessors can only provide their best guess about implementation, but it is this contextualisation of “evidence” that makes HTA such an essential tool to decision making.

Communicating results in an HTA

As illustrated, interpreting the results of an HTA is complex. Knowing that the end users are not always able to digest a full technical report – which can run to hundreds of pages – the assessor must therefore summarise the results accurately and succinctly. Specifically, this often means using dot points, summarising in tables or figures, and making tough decisions about what information should go “up front” in a report.

In recent years primary research communication, has gained from the advent of visual abstracts and now, influential, international journals such as the BMJ and JAMA routinely

publish them. Visual abstracts are not intended to replace reading the full article but to attract the reader’s interest. Usually, they summarise methods and results, but rarely study limitations. They are also a useful means of communicating medical research on social media. Ramos and Concepcion (2020) reported that social media posts with visual abstracts had higher engagement rates than posts without pictures or than other types of visual post (such as tables or graphs from the study).⁷ Whilst this engagement

is desirable, the authors also acknowledge that the succinct nature of a visual abstract could lead to misinterpretation and oversimplification of the study results. Oversimplification is a major risk when presenting the results of an HTA if the uncertainty associated with the results is not communicated.

A key way of communicating uncertainty in the clinical component is to use GRADE (Grades

Being clear, direct, and comprehensive in describing the findings of an HTA is vitally important to both the utility of the work and to its trustworthiness.

of Recommendation, Assessment, Development, and Evaluation).⁸ This tool, designed for guideline developers, enables assessors to appraise the quality of the evidence by outcome, taking into account factors such as the risk of bias in the included studies, inconsistency, and publication bias. In the US, the Agency for Healthcare Research and Quality have a similar tool.⁹ Although GRADE is widely used, it is not without its issues, particularly around automatic downgrading of observational studies. Moreover, although it can provide information about strength of evidence for individual outcomes, it does not provide an overall assessment of the intervention, taking into account all the possible benefits and harms. In HTA, findings need to be communicated across a range of desirable and undesirable outcomes and decisions made on whether the benefits of an intervention outweighs the harms, within the context of the proposed clinical setting.

The key aspect of all forms of communication of results is transparency. This is especially true for uncertainty, as it is more difficult to communicate and understand than simple “results”.

Considerable work has been done to assess the best way to present results, especially to patients, but the best way to communicate any uncertainty associated with those results is much more difficult and has not been studied extensively. Uncertainty in findings may or may not influence decisions, but it always needs to be considered. Being clear, direct, and comprehensive in describing the findings of an HTA is vitally important to both the utility of the work and to its trustworthiness. The documentation of all methods (such as the choice of inputs for economic models, reasons for downgrading or upgrading of evidence) and their justification is essential to ensure that end users are properly informed for decision making.

Comprehensive explanations can rarely be summarised in dot points, however – and herein lies the issue. How do we communicate the important aspects of uncertainty in an HTA in a way that is succinct but understandable? Tools like GRADE use a visual representation of solid and hollow circles to illustrate certainty for individual outcomes. When considering a whole HTA (with clinical, applicability and economic outcomes) a succinct visual tool is needed to express the heterogeneity of uncertainty across all parameters. Today, there is no standard method for representing uncertainty, and further research is required to determine a suitable method. Some ideas include a visual representation of uncertainty, such as a traffic light system, alongside key results, or using different colour or font text for different levels of uncertainty. This could be especially helpful for interpreting the results of economic analyses.

On the other hand, we need to be careful that we do not fall into the trap of oversimplifying results. HTAs are complex and technical, and explanations that provide adequate transparency can be necessarily lengthy. We need to strike a balance between thorough reporting of results – including uncertainty – and summaries that are useful and accurate.

Some of the issues to consider when communicating results of an HTA are explained in Table 1. This list is by no means exhaustive but may provide a starting point for medical writers to think about how they can contribute to transparency and the understanding of the limitations of an evidence base.

HTAs are an increasingly important tool in decision making worldwide, and their methodology has developed, and continues to develop,

alongside this growth. To ensure the greatest utility and to encourage trust in HTA, we must continue to work towards complete transparency when reporting all aspects of the HTA. Policy makers and funders also need to be transparent in their decision-making processes. As HTAs are often read only in summary form, medical writers need to carefully consider how uncertainty associated with the findings in abridged versions of reports is conveyed. Uncertainty does not need to be a sign of weakness, and an acknowledgement that it exists and a description of how it has been approached add credibility to research. As the battle against misinformation and mistrust in science rages on, it has never been more important to be transparent and trustworthy.

Disclaimers

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

Conflicts of interest

The author declares no conflicts of interest.

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Reporting health economic evaluations: CHEERS and beyond



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Abstract

Health economic evaluations are relevant to those making healthcare resource allocation decisions, such as listing a new drug on the national formulary or launching a new vaccination programme. Compared with clinical studies that report only the health consequences of an intervention, economic evaluations require more space to report additional items such as resource use, costs, preference-related information, and cost-effectiveness results. This creates challenges

for editors, peer reviewers, and those who wish to scrutinise a study's findings. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) updated previous efforts to produce a single useful reporting standard. It received endorsement from, and was co-published in, 10 journals that frequently publish health economic evaluations. CHEERS provides a sound basis for improving the reporting of economic evaluations.

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Introduction

Health economic evaluation is defined as ‘the comparative analysis of alternative courses of action in terms of both their costs and their consequences’.¹ These evaluations are increasingly used for decision-making and are an important component of health technology assessment (HTA) programmes internationally.² The need for economic evaluations to report both health consequences of an intervention and additional items on resource use, costs, preference-related information, and cost-effectiveness results creates a challenge for editors, peer reviewers, and those who wish to scrutinise a study’s findings.³

There is evidence that the quality of reporting of economic evaluations varies widely and could benefit from improved quality assurance mechanisms.^{4,5} Transparency and structure in reporting is especially relevant for health economic evaluations because:

1. the number of published studies continues to grow;⁶
2. there are potentially major consequences from resource allocation decisions based on misleading study findings; and
3. unlike clinical trials, there are no widely-implemented mechanisms for registering studies or making data available for independent interrogation or analysis.

Endorsement of reporting guidelines by journals has been shown to improve reporting of clinical research.⁷ The risk of making costly

The risk of making costly decisions due to poor reporting combined with the lack of mechanisms that promote accountability, makes transparency in reporting economic evaluations especially important and a primary concern among journal editors and decision-makers.

decisions due to poor reporting combined with the lack of mechanisms that promote accountability, makes transparency in reporting economic evaluations especially important and a primary concern among journal editors and decision-makers.^{3,8}

Development of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)

Following the recommendations of a previous task force,⁹ the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) established the CHEERS Task Force to improve the reporting of health economic evaluations. Task Force membership consisted of health economic journal editors and content experts from around the world. The Task Force used a process consistent with that used in the development of the EQUATOR suite of guidelines, such as CONSORT (for the reporting of clinical trials) and PRISMA (for the reporting of systematic reviews). This involved consulting a Delphi group consisting of international experts representing academia, biomedical journal editors, the pharmaceutical industry, government decision makers, and those in clinical practice.

CHEERS aimed to consolidate and update previous efforts¹⁰⁻²¹ into a single useful reporting standard. It received endorsement from, and was

co-published in, 10 journals that frequently publish economic evaluations. The CHEERS reporting standard is not intended to prescribe how economic evaluations should be conducted; rather, analysts should have the freedom to innovate or make their own methodological choices. Its objective is to ensure these choices are clearly reported to reviewers and readers. Therefore, the CHEERS statement could be used to examine the quality of reporting, but it is not intended to assess the quality of study methods (other checklists have been developed for this purpose).²² The primary audience for the CHEERS reporting standard are researchers reporting economic evaluations, journal editors, and peer reviewers of the intended journals. CHEERS consists of a 24-item checklist accompanied by recommendations on the minimum amount of information to be included when reporting economic evaluations. It has been adopted as an EQUATOR guideline.

The CHEERS checklist

The CHEERS checklist was published in 2013 and is shown in Table 1. In the full explanation and elaboration document,²³ which can be downloaded from the ISPOR website ([https://www.ispor.org/heor-resources/good-practices/article/consolidated-health-economic-evaluation-reporting-standards-\(cheers\)-explanation-and-elaboration](https://www.ispor.org/heor-resources/good-practices/article/consolidated-health-economic-evaluation-reporting-standards-(cheers)-explanation-and-elaboration)), the rationale for each of the 24 items is explained and examples given. [See Table 1 on pages 62–3]

Continued on page 64

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Table 1. CHEERS checklist: Items to include when reporting economic evaluations of health interventions

Section/Item	Item No.	Recommendation	Reported on Page no. / Line No.
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	

Section/Item	Item No.	Recommendation	Reported on Page No. / Line No.
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytic model.	
Analytic methods	17	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data, extrapolation methods, methods for pooling data, approaches to validate or make adjustments (e.g., half-cycle corrections) to a model, and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness and incremental cost-effectiveness, together with the impact of methodological assumptions (e.g. discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of Interest	24	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.	

Source: Husereau et al.²³

Item 3: Introduction

Recommendation: Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.

Example:

Many nonsurgical treatments, such as decongestants, antihistamines, antibiotics, mucolytics, steroids, and autoinflation, are currently used in the UK National Health Service (NHS) as short-term treatments for otitis media (OME) in an attempt to avoid unnecessary secondary referral and costly surgery. However, there is little evidence that these nonsurgical options are beneficial. 'further evaluation should aim to estimate the cost-effectiveness of topical intranasal corticosteroids in order to provide decision-makers with evidence on whether the considerable resources currently being invested in this area represent an efficient use of scarce public resources' ... 'This paper summarises the methods and results of an economic evaluation that was based on evidence from the GNOME trial (p543)'²⁴



Explanation: Economic evaluations may examine whether a new intervention should be reimbursed or may assess existing health interventions. Sometimes, a resource allocation question will be researcher- or consumer-driven. Increasingly, however, economic evaluations are being conducted to meet the needs of decision-makers who need to understand the consequences of re-allocating healthcare resources. If the study was conducted for a decision maker, this should be stated. Otherwise, a description of the importance of the question should be given. It is not enough to state that "The purpose of the study was to assess the cost-effectiveness of treatment X". Correct specification of the study

question requires details of the study (patient population, the intervention of interest, the relevant comparator(s), and the healthcare setting). Therefore, reporting on this item needs to be considered in conjunction with that for CHEERS checklist items 4–7 (i.e. target population and subgroups; setting and location; study perspective; and comparators) described below. A good example of a study question would be "We assessed the cost-effectiveness of etanercept, as compared with infliximab, in patients whose rheumatoid arthritis was inadequately controlled by methotrexate, within the context of the UK National Health Service".

Examples of CHEERS items #3 and #6.

Continued from page 61

Updating CHEERS

Study methods and reporting standards may change over time, and many of the established reporting guidelines, such as CONSORT and PRISMA, have been updated periodically. In 2020, ISPOR decided to update CHEERS, and the Task Force was reconvened. A number of factors led to the update. First, feedback on the CHEERS checklist suggested that it was inadequate for reporting studies such as cost-benefit analyses, which measure and value benefits in monetary terms.²⁷ In addition, a study of the use of the CHEERS checklist suggested that it was often used inappropriately. Specifically, it was often used to assess the methodological quality of published studies, rather than the quality of reporting.²⁸

There have been several important developments in the methodology of economic evaluation that necessitated modification of the current checklist.

Second, there have been several important developments in the methodology of economic evaluation that necessitated modification of the current checklist. These include developments in the methods for assessing individuals' preferences for health and healthcare, more complex approaches to modelling and the characterisation of uncertainty, and a growing interest in the distributive effects (i.e. impacts on equity) within economic evaluations.

Third, there has been a growing interest in the contribution of patients and the general public in designing and conducting health services research studies, including economic evaluations. Patients and the general public are also increasingly important audiences for the results of economic evaluations, given their participation as stakeholders in health technology assessment (HTA) processes in many jurisdictions. There-

fore, they are interested in knowing which groups of patients the study results apply to, whether outcomes relevant to patients have been assessed, and whether patients have been consulted on the design of the study.

The revision of CHEERS, which is ongoing, will respond to these developments. The Task Force includes new members with the relevant expertise in the main methodological developments and is being advised by a Patient and Public Involvement and Engagement Group with plans to report these efforts using the GRIPP2 guidelines for patient engagement.²⁹ The revised CHEERS checklist will be published in 2022 and will be endorsed by a number of journals, including those who are the largest publishers of economic evaluations.

Concluding remarks

Adequate reporting of research is crucial, especially in applied areas of research. Excellent research that is poorly reported helps no one. This has been recognised by researchers in health economic evaluation, and the CHEERS guide-

Item 6: Study Perspective

Recommendation: Describe the perspective of the study and relate this to the costs being evaluated.

Example 1:

The cost of implementing each intervention is derived from an Australian health sector perspective. This includes costs to both government and patients, including time and travel costs, but excluding patient time costs associated with changes in physical activity. Intervention start-up costs (e.g. costs of research and development of intervention materials for GP prescription) are excluded so that all interventions are evaluated and compared as if operating under steady-state conditions... (p2)²⁵

Example 2: “Estimates of direct costs associated with each type of surgery were derived from the perspective of the payer and included hospital charges and professional fees for the initial operation as well as those for any subsequent services or procedures that might be necessary to manage postoperative complications.”²⁶



Explanation: The study perspective is the viewpoint from which the intervention's costs and consequences are evaluated. A study could be conducted from one or more perspectives, including a patient perspective, an institutional perspective (e.g. hospital perspective), a healthcare payer's perspective (e.g. sickness fund, Medicare in the United States), a healthcare system perspective, a public health perspective, or a societal perspective. Most studies are conducted from a health system or payer

perspective (e.g. NHS in England, Medicare in the United States) or from a societal perspective. The health system and payer's perspectives typically include direct medical care costs, including the cost of the intervention itself and follow-up treatment costs.

A societal perspective will also estimate broader costs to society (e.g. productivity losses resulting from poor health or premature death, family costs, or costs to other sectors such as the criminal justice system). Because these perspectives lack standard definitions, authors should describe the perspective (e.g. healthcare system, societal) in terms of costs included and their associated components (e.g. direct medical costs, direct non-medical costs, indirect/productivity costs), and how this fits the needs of the target audience(s) and decision problem. When a societal perspective is used, reporting the results from a healthcare system or payer perspective, where only direct medical costs are reported, should also be considered. References to jurisdiction-specific guidelines or documents describing local economic evaluation methods can also be provided, along with a reason for why these were chosen.

lines have been developed to provide an international standard for study sponsors, medical writers, authors and journals consistent with the accepted methodology for EQUATOR guidelines. The CHEERS Task Force recognises that publishing economic evaluations with sufficient information to allow interpretation and replication is quite challenging, as it requires a significant amount of text. However, the Task Force also assumes these demands are becoming easier to meet as online supplementary information can be submitted to journals, and open data sharing has become more commonplace. The Task Force anticipates the update will provide an even more useful tool for authors and medical writers in the coming years.

Conflicts of interest

The authors are members of the CHEERS Task Force. They have no other conflicts to declare.

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The medical writer's role in health technology assessment submissions

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Abstract

Writing health technology assessment (HTA) submissions is a challenging and rewarding area of medical writing, being part of the process of giving patients access to new medicines. Submission requirements differ between countries but all require clear communication of the new product's value. This article looks at the medical writer's role in UK and German submissions, but many of the points covered will be generalisable to other jurisdictions.

Health technology assessments (HTA) help inform payer decisions about what medicines and other technologies to fund, and at what price. These may be carried out by official national bodies, such as England's National Institute for Health and Care Excellence (NICE), France's National Authority for Health (HAS), and Germany's Federal Joint Committee (G-BA), or at local and regional levels. Medical writers play an important role in the writing and managing of dossiers submitted by manufacturers to the decision-making bodies. This article outlines the medical writer's role in HTA submissions (also known as reimbursement submissions) and examines how we can add value in the quest for a successful appraisal, one which culminates in patient access to novel medicines and reimbursement at a satisfactory price for both the manufacturer and the health system.

Writing HTA submissions is a challenging and rewarding role that sits somewhere between



regulatory medical writing and medical communications. The medical writer is a key part of a submission team that also includes health economists, data analysts, market access professionals, and systematic reviewers. HTA

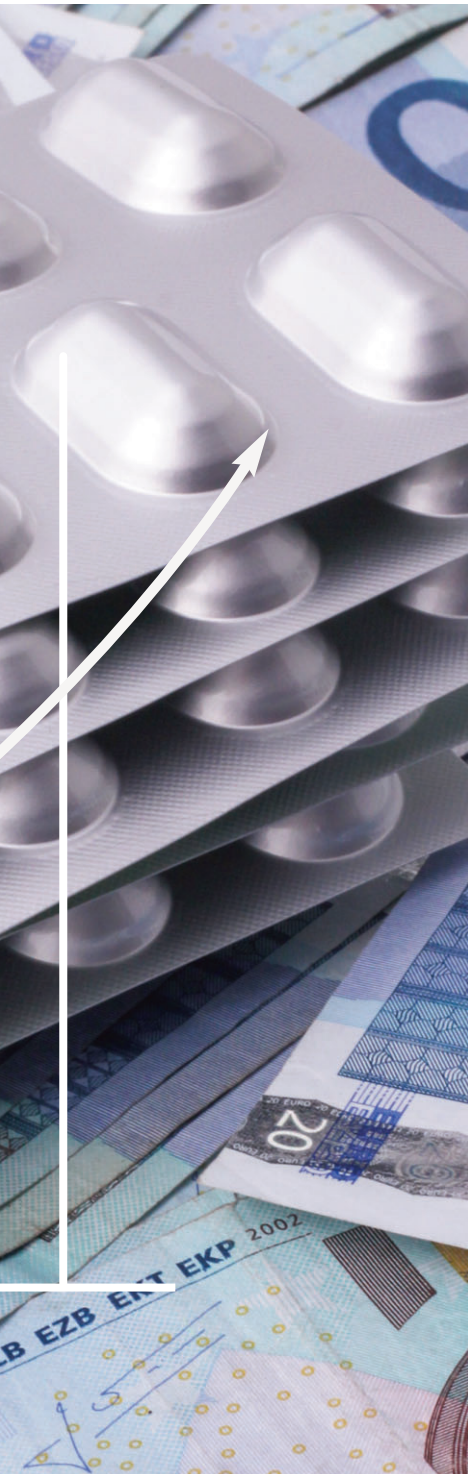


Photo: Marek Studzinski

submissions are sometimes handled in-house by the pharmaceutical or device company, but more typically the sponsor company (often called the “manufacturer”) will engage a consultancy to carry out the economic modelling, advise on strategy, and create the submission dossier. This article is written from the perspective of the authors’ experience in writing UK and Irish HTA submissions (to NICE, the Scottish Medicines Consortium, All Wales Medicines Strategy Group, and the National Committee for Pharmacoeconomics), but many of the principles covered are transferrable to other jurisdictions. Tina Krieger looks more closely at the writer’s role in German HTA submissions.

What makes a good HTA submission?

In the UK system – and in a few other countries including the Netherlands, Sweden, Canada, and Australia – economic modelling is central to the HTA process. In the UK, this takes the form of cost-effectiveness analysis. Health economists attempt to represent the disease and its treatment within established modelling approaches such as Markov models or partitioned survival analyses. The primary inputs to these economic models are the relative efficacy of the treatment under assessment versus the designated comparators (the current treatments that the new technology would be expected to displace), the costs of the treatments (including acquisition costs but also the costs of administration, monitoring, treatment of adverse events, and any other costs or cost savings associated with the treatments), and the effects of the different choices on patients’ health-related quality of life (HRQoL). These are (usually) modelled over a lifetime horizon, requiring the use of statistical techniques to extrapolate beyond the term of the trial.

However, the HTA submission is more than just the economic modelling. A good submission dossier has a consistent narrative that argues the case for the new treatment – from the burden of the disease and the unmet medical need, through to the benefits of the new treatment to patients, its innovative nature (if applicable), and why it represents a good use of healthcare resources. In addition, the clinical evidence and the economic modelling must both be clearly communicated, and someone must manage the dossier.

The medical writer is typically responsible for all of these aspects.

The medical writer’s role

The medical writer’s role in HTA submissions has three main aspects: populating the clinical sections of the dossier template, supporting the health economists/analysts, and managing the dossier. We will now look at each of these more closely.

Writing the clinical section

Each HTA body has its own submission template and an accompanying user guide. Be sure to download these freshly for each submission in case there have been changes, and follow the user guide carefully.

To write a successful clinical section, the writer must gain a good understanding of the disease area, the current treatment pathway, and the new treatment and its trial data. From this, it is essential to construct a clear “value story”. What is the unmet medical need? How does this product address it? What advantages (i.e., what “added value”) does it offer over current treatment – to patients, caregivers, health services, and (perhaps) from a societal perspective? Sometimes the manufacturer will already have a clear story and may have developed materials such as a global value dossier to help communicate it. But in a drive to give patients access to new medicines as quickly

A good submission has a consistent narrative that brings out the product’s value.

as possible, HTA dossiers are often prepared before regulatory approval has been granted, and sometimes no clear value story has been set out. It is important to be clear on these issues within the submission team, or the submission will lack a coherent argument. The clinical section of the submission should give a balanced picture of the health condition but should focus particularly on the needs that the new product meets, from both the patient and the healthcare system perspectives. It is also crucial for the medical writer to understand how the condition is going to be represented in the economic model. For example, the health states in an economic model of HIV might be based on CD4+ cell count. The clinical section of the submission must therefore explain the importance of the CD4+ count and its relationship to clinical outcomes and health-related quality of life.

Furthermore, it is important to define the population for which the new technology should be funded, and to provide an estimate of population size. Linked to this, there must be a clear description of the current treatment pathway based on national clinical guidelines and protocols, and of where in the pathway the technology will sit and what (if any) current treatments it is expected to displace. These treatments are known as the comparators. Unlike clinical trials, where there is typically a single comparator, payers compare new technologies against all current treatments.

The clinical section of the dossier also presents the pivotal clinical trial. This section should give the HTA body a clear understanding of the trial methodology and population so that they can critically appraise the results. The medical writer must use their judgement about what to include, within the template requirements. Decision-making committees have limited time to spend on each submission, so the case must be made clearly and succinctly. However, in most jurisdictions the submission will also be scrutinised by a technical review body that will advise the committee, so they must be given sufficient detail to form a good understanding. The key question is "Will this information aid the payer in their decision-making?", either as key data or as context. If not, better to leave it out so that the core narrative does not get lost in a welter of additional detail. The Clinical Study Report will usually be supplied as a reference.

The final element of the clinical section focuses on interpretation and contextualisation of the clinical data. It is important to show payers that the trial data are representative of the likely effects in the local real-world population. How generalisable are the trial data to the health system in question? Is the trial population comparable to patients who will receive the technology in local clinical practice? This can be addressed by comparing the population with that of country-specific registries or publications of large national or regional case series. Any differences should be explored and contextualised, for example by comparing outcomes in the comparator arm with those from more representative trials or series. Any evidence gaps, such as the absence of head-to-head data

Frequent cross-talk between writing and modelling teams is needed to optimise the submission.



versus one or more comparators or a lack of data on health-related quality of life, should be stated, and the way that these issues will be addressed in the submission should be explained. This means working closely with the health economics team to understand the approach being taken so that the clinical section provides the information and argumentation needed to support it. Close cooperation with the team at the sponsor company is also important.

Medical writers also have an important role in the post-submission phase, which involves providing clarifications and responses to questions from the HTA body.

Supporting the health economics team

As a result of researching and writing the clinical section, the medical writer is usually the team member with the most knowledge of the disease and its treatment. Writers can thus be an important sounding board for health economists when the latter are developing modelling assumptions and inputs (validation of the modelling approach by clinical experts is also key). Frequent cross-talk between the writing and modelling teams improves the ability of both specialisms to optimise the overall submission and can avert problems such as the modelling team using an assumption that is open to clinical challenge. Writers need to be able to spot when arguments made in the economic section are not compatible with those in the

clinical section – or vice versa – so that conflicts can be resolved early.

The economic section of the submission template is usually drafted by the health economists, but the medical writer should review it from both a communication and an editorial standpoint to ensure that the economic concepts are clearly communicated and are anchored in the relevant literature and guidelines.

Managing the dossier

The medical writer will typically have editorial responsibility for the dossier, including formatting, confidentiality marking, and creation of the reference pack. This can be time-consuming, and it is important to allow sufficient time for dossier finalisation in the project plan.

Medical writing for German reimbursement submissions

The German process is not an HTA process *per se* as usually no economic evaluation is required. Therefore, I will refer to the dossier as a reimbursement dossier. As described by Kohler & Christoph in this issue of *Medical Writing* (p. 22), new drugs are reimbursed in Germany as soon as they receive marketing authorisation; (see the article for further details of the German reimbursement process). A reimbursement dossier needs to be submitted to the German G-BA on the day the product is brought onto the market, or within 3 months in the case of a new indication for an approved drug. The pharmaceutical drug is compared against an appropriate comparative therapy (ACT); this

contrasts with the NICE process, where all drugs approved in the indication are taken into consideration.

The G-BA sends all reimbursement dossiers for non-orphan drugs to the Institute for Quality and Efficiency in Health Care (IQWiG) for assessment. IQWiG provides recommendations within 3 months on the additional benefit of the drug. The extent of the additional benefit is the basis for the price negotiation with the statutory health insurance (SHI). For orphan drugs, the assessment is done directly by the G-BA.

The reimbursement process starts before dossier submission. The G-BA provides the opportunity to address specific questions in an early advice meeting. An application needs to be completed prior to the meeting where all questions relating to the submission can be put, specifically which is considered the appropriate therapy, whether trial design can be considered appropriate, the patient relevance of endpoints, or whether the subgroups have been chosen correctly based on the data available. The pharmaceutical company should provide its response with all the arguments for or against a specific statement. Preparing this application requires a lot of discussion, research, and medical writing. The submission team members discuss and agree upon what questions to ask and research the replies. The research for these questions includes the review of recent national (or where not available, European or international) guidelines, to identify the ACT, and the identification of previous assessments in this or a similar indication to identify whether the endpoints chosen are patient-relevant, or to address other questions of interest.

There is a template for the reimbursement dossier on the G-BA website. The dossier consists of five modules (see Kohler & Christoph) and

must be submitted in German. Module 1 is a summary of modules 2 to 4 with word restrictions and is comparable to the NICE document A. Module 5 contains all the references cited in modules 1 to 4. Module 2 is a rather small document and contains general information such as the drug's mode of action and the approved indications. The information is usually found in the Summary of Product Characteristic and in regulatory documents.

More information needs to be provided in module 3. The ACT needs to be named and its appropriateness justified. The derivation of the patient population is an important section and of interest for the price negotiation later in the process. The attention is on the target population and specifically the population for which an additional benefit is expected. The [destatis.de](https://www.destatis.de/DE/Home/_inhalt.html) website (https://www.destatis.de/DE/Home/_inhalt.html) is a good source to get overall patient numbers, with more specific numbers provided by trial registries or in the published literature. This module also contains a section on the cost of the therapy and its ACT, which are listed in the Lauer-Taxe database (not free of charge).

Module 4 contains the results – the medical benefit and the medical added benefit when comparing to the ACT. The result section is the critical part of the submission together with the section about the final assessment of the additional benefit, including its probability from the pharmaceutical company's view. These sections require a lot of medical writing as all the results for all endpoints measured in the described trials, preferably randomised controlled trials, need to be presented and interpreted. The primary sources of information are the clinical study reports available for the drug of interest and any published literature on

the drug of interest and the ACT.

Once the reimbursement dossier is submitted, the preparation for the written statements starts; the purpose of this statement is to provide responses or clarifications to points in the IQWiG assessment, where this is considered necessary. There are only 3 weeks between the publication of the IQWiG assessment on the G-BA website and the possibility to provide written statements to the G-BA. It is advisable to summarise all possible points that may need to be addressed and prepare for them in advance. After submitting the written statements, the pharmaceutical company receives a date for an oral hearing at the G-BA for which preparations are also required. The company must prepare for different scenarios that might emerge during the meeting, and the medical writer is often involved in researching and formulating responses. The G-BA decides on the additional benefit considering the IQWiG assessment, the written statements, and the outcome of the oral hearing. The writing work on German submissions is quite challenging as there is no economic modelling, so the case for the degree of additional benefit is made solely on the basis of clinical efficacy.

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HTA decision-making: Do ethics matter?

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Abstract

Before reviewing the article in this issue of *Medical Writing* by Larry Liberti and Tina Wang, *The regulatory-HTA decision-making interface: What the medical writer should know* (p. 50), I put on my ethicist's hat. Thus, I tuned my ethics antennae to detect whether there might be some concerns about issues that could result in unintended harm, either to individual patients, or to the collective society to which health technology assessment (HTA) and regulatory authority decisions might apply. I approached the evaluation as an opportunity to ask questions that should be considered, rather than suggest solutions. This may better enable those charged with making critical healthcare decisions to evaluate choices in context, rather than attempt to apply overarching "rules". This approach, of course, raises the challenge of whether it is appropriate to apply "situational ethics", or whether there should, indeed, be universal standards that should remain inviolable and absolute. Perhaps, this is where objective algorithms must be melded with subjective human assessments, based on education, experience, expertise, personal values, and instinct. Hopefully, this will stimulate thoughtful questions in the context of HTAs, and medical writers will better understand the scope of medical decision-making. In this way, we may raise awareness, and hopefully, prevent – or at least recognise – the potential for harmful unintended consequences of certain HTA-based medical decisions.

The EUnetHTA HTA Core Model

The International Network of Agencies for Health Technology Assessment (INAHTA) Working Group on Ethical Issues has identified and defined various methodological approaches that are used by HTA agencies.¹ The European Network for Health Technology Assessment (EUnetHTA) HTA Core Model (version 3.0), mentioned in the article by Liberti and Wang,² recognises ethical aspects of health technologies, which should be considered in an HTA Core Model. As noted in this document, "Ethics ... has a broader application within the field of HTA. The assessments themselves should be designed in such a way that key ethical principles are considered and respected". EUnetHTA also raises an overarching question of whether there are ethical issues related to the consequences of performing the HTA.

These principles reflect the protection of human rights first established by the Nuremberg Code (1947),³ and progressively embodied in subsequent declarations, including the Declaration of Helsinki (1964, updated most recently in 2013);⁴ The Belmont Report (1974);⁵ and Regulation (EU) No 536/2014 of the European Parliament and of the Council (2014).⁶ In addition, the International Council of Harmonisation (ICH) has embodied many of these principles into their Good Clinical Practices guidance.^{7,8}

In each case, there are six primary principles that should be evaluated:

1. Benefit-harm balance
2. Autonomy
3. Respect for persons
4. Justice and equity
5. Legislation
6. Ethical consequences of the HTA

In reviewing these principles, it is important to keep four key concepts in mind:

1. The ethics of product vs. the ethics of process
2. The interests of the individual patient vs. the interests of society
3. The differences between practice and research
4. The economic vs. therapeutic value

It is important to recognise that there may be inherent conflicts (or at least, dynamic tensions) in attempting to satisfy both considerations in each of these examples. Thus, in evaluating applications, questions arise concerning these concepts, all of which may be applied in the assessments:

- What are the trade-offs between the benefits to the patient vs. those to society?
- Should approval or denial of funding new therapies be based on cost alone?
- Are end-of-life years more or less valuable than those at earlier stages?
- Should negative or inconclusive data be considered when one believes that these data may represent an exception?
- Is there a risk of decision-maker bias, incorporating *a priori* assumptions about the interventions being evaluated, as well as the understanding of the HTA goals?

While I will not address all of the aspects mentioned above, I have selected those topics that I believe are most germane to the medical writer.

Benefit-harm balance – accelerating access to new therapies and vaccines

These are strange times, and in the midst of a pandemic, the "normal" standards of proof and determination of the benefit-harm balance may have to be adjusted. Liberti and Wang note that "a new challenge has emerged with the preponderance of new innovative products that are receiving regulatory authorisation where there is an unmet medical need, and therefore, few therapeutic alternatives. Using facilitated regulatory pathways (FRPs) such as the breakthrough therapy designation, priority and accelerated reviews, and conditional marketing authorisations, important new therapeutic options with good signals of clinical efficacy are being approved in record times".² This has come into sharp relief in the context of the COVID-19 pandemic. I have previously written about the potential harms associated with some forms of pre-approval access, most notably, those associated with pathways facilitated by the Right-to-Try Act in the USA, and the Saatchi Bill in the UK.⁹



As Liberti and Wang state, “... the paucity of long-term data – and therefore the reliance on surrogate endpoints for the regulatory decision – make formulating a value recommendation complicated”.² I certainly agree, and we must confront concerns, in the context of desperation, about whether some of the standards of empirical research should be compromised, in the interest of making potentially life-saving therapies and vaccines available earlier than they might be otherwise. Furthermore, we must confront such concerns with an acknowledged acceptance of the potential for increased risk (primarily due to the “unknown unknowns”) assumed when we “lower the bar”. Is it legitimate to create “one-off” regulatory standards? What are the consequences? In this context, how are the probability of harm and possibility of benefit adequately conveyed in informed consent, when the testing process has been accelerated? How will we communicate to the public and prescribers about therapies/ vaccines that have been “approved” based on lower standards?

This raises the topic of “situational ethics”. Do desperate times require desperate measures? Is “no science” worse than “bad science”? In this time of great global peril, when countless lives are being held in the balance, are we willing to lower the threshold of scientific integrity for the sake of accelerating the availability of speculative

medicinal products?

These compromises may even occur outside of the context of a pandemic, as demonstrated by the recent FDA approval of aducanumab for Alzheimer’s disease.¹⁰ In my opinion (and that of the independent advisory committee) the evidence that its manufacturer, Biogen, submitted to the FDA showed no convincing effect on patients’ cognitive decline. Its two main trials were stopped early in 2019 because Biogen concluded that its drug did not work. Reanalysis, using questionable surrogate endpoints based on a putative association between myeloid plaque levels and cognitive function, resulted in approval, despite concerns about brain swelling and haemorrhage associated with higher doses of the drug. Thus, there are issues of raising false hope in patients and their families, thereby

increasing risk; and given the high cost of the drug (monthly infusions with a US\$56,000 annual price tag, and the need for regular MRI scans to monitor for brain swelling), an added financial burden.

There is no question that bad science does not deserve a forum. However, good science needs to be heard, even if some people will twist its meaning. Hopefully, scientists desire the safest and most effective treatment or vaccine and the most reliable diagnostic possible, but these cannot be refined if researchers ignore inconve-

There is no question that bad science does not deserve a forum.

However, good science needs to be heard, even if some people will twist its meaning.

nient data. Moreover, scientists will earn a lot more public trust, and overcome a lot more unfounded fear, if they choose transparency over censorship. As Jacci Parsons¹¹ points out in her article, “The key aspect of all forms of communication of results is transparency. This is especially true for uncertainty, as it is more difficult to communicate and more difficult to understand than simple ‘results’”. After all, research is a building-block process. There is no crystal ball into which we may gaze to determine absolute truth. Technological advances and human insights will open the doors to a better understanding of processes that had been hidden from us in the past.

Even in the traditional course of research, development, and approval of novel therapeutics, there are often late-emerging untoward sequelae – signals that emerge only after a drug has been commercially available and administered for years after approval. One needs only recall Pfizer’s withdrawal of Bextra from the US market on recommendation by the FDA, citing an increased risk of heart attack and stroke, as well as the risk of a serious, sometimes fatal, skin reaction. Other examples include Zelnorm, withdrawn based on evidence that it raised the risk of heart attacks and strokes; and ketoconazole-related cardiac arrhythmias associated with Seldane and Hismanal, resulting in the addition of “black box” warnings to their product labels. It is interesting that the majority of cases of product withdrawal are due to cardiovascular safety concerns.

In the context of designing a clinical trial, should benefit-harm ratios be established when considering comparators? If the benefit-risk ratio falls below a certain threshold, should the patient be allowed to be treated with the investigational product?

Autonomy

Overlaying this discussion is the principle of individual agency – the capacity for human beings to make choices and impose those choices on the world. This should be distinguished from the concept of “free will”, as these choices are not to be influenced by outside forces. This is important in determining the degree of protection from undue influence in making critical healthcare decisions. Of course, we are not computers, driven by algorithms, and there will always be a

degree of influence, sometimes to our benefit. For example, it is wise to seek counsel of a “learned intermediary”, who may be well-versed in the complexities of a particular disease and its treatment options. This subject matter expert may then serve as an advocate or adviser. Human agency invests a moral component into a given situation. If a situation is the consequence of human decision-making, persons may be under a duty to apply value judgements to the consequences of their decisions and be held responsible for those decisions. This concept applies to societies as well as individuals. Governments have the ability to make decisions about what they believe is best for their citizens, and by extension, the world. Sadly, political considerations will almost always colour these decisions.

Another aspect is the exercise of autonomy by clinicians, in terms of accepting what may be limited data, including some that may be anecdotal. There are very clear distinctions between medical practice and medical research, and these may not be clearly understood by patients, and in many cases, clinicians. These have been articulated in the Belmont Report.⁴ Practice consists of “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioural practice is to provide diagnosis, preventive treatment, or therapy to particular individuals”. Research is an “activity designed to test a hypothesis, permit conclusions to be drawn, and thereby, to develop or contribute to generalisable knowledge. Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective”.

How do, or should, we counter the tendency to believe in information based on sub-standard sources (e.g., those for which no solid empirical evidence exists)? Are the “gold standard” randomised, controlled, clinical trials a required evidentiary standard in the teeth of a pandemic?

Decision-making

In the previous section, I addressed the quality of data used to make the critical decisions facing regulators, HTAs, physicians, and patients. One

might first consider a hierarchy of “admissible evidence”, based on legal concepts applicable to a court of law:

Anecdote ► Data ► Evidence ► Admissible evidence

Anecdotes are unstructured. Data have structure but may contain irrelevant or misleading information. Evidence requires an analysis of the data with an objective of proof. “Clear evidence is positive, precise, and explicit, as opposed to ambiguous, equivocal, or contradictory proof, and which tends directly to establish the point to which it is adduced, instead of leaving it a matter of conjecture or presumption, and is sufficient to make out a *prima facie* case”.¹²

Decisions are often made without applying rigorous decision-making tools, such as the 8-step medical/regulatory decision-making tool, the Universal Methodology for Benefit-Risk Assessment (UMBRA), developed by the Centre for Innovation in Regulatory Science (CIRS).¹³ However, even when such tools are used, much of the process allows for subjective input by individuals involved in the process of weighting and grading of factors, which are used to guide decision-making.

Newly evolving studies of the neurocognitive bases for decision-making may shed further light on how we might improve the processes and outcomes associated with critical decisions.

Newly evolving studies of the neurocognitive bases for decision-making may shed further light on how we might improve the processes and outcomes associated with critical decisions. This research may be particularly valuable, as it incorporates economics into the paradigm. In the context of the HTA, where consideration is given not just to the therapeutic profile, but the economic

impact of reimbursement, this might have meaningful consequences.¹⁴ As noted in Wendy J. Babidge’s article,¹⁵ in this issue of *Medical Writing*, (see p. 16) companion concepts include increasing reliance on evidence-based medicine, real-world data (RWD), and real-world evidence (RWE).

Justice and equity – individual vs. society

At the outset, it is important to recognise that, at the interface of institutional healthcare decisions, there will often be a dynamic tension between

the individual patient and society. This often is a result of limitations on resources – financial, therapeutic, and personnel – which must be drawn upon to serve the needs of citizens. Thus, all needs of all people can seldom be met, and this means that the calculus of “the greatest good to the greatest number” will usually be applied.

Perhaps the most relevant issue with respect to justice and equity, aside from ensuring that there is no discrimination in the availability of healthcare, based on socioeconomic or racial characteristics, is the fundamental dynamic tension between the individual and society. There are, necessarily, trade-offs between potential value to be gained by each of these entities. Thus, one must consider if, as an individual member of society, one has an obligation to the greater good of the greater number of that group to which one belongs. This concept applies to both personal obligations and personal liberties. We obey laws and societal conventions, not because they necessarily have great potential benefit to us (not robbing the local bank, for example), but because they form the underpinnings of a functioning society. We also have protective laws in place that constrain unwarranted actions by society (e.g., laws against illegal search-and-seizure).

Likewise, governmental agencies, which provide the funding (via taxpayers, of course) for healthcare – including reimbursement for the cost of drugs – must consider themselves stewards acting on behalf of both individuals and groups within their citizenry. Fundamental economics stipulate that there are not enough resources to serve all the needs of each citizen, resulting in the need to make difficult decisions about where to allocate funds that provide the optimum affordable coverage. In a sense, this runs counter to situational ethics, in that there are few opportunities, let alone capacity, to consider individual cases on their own merit. Thus, more generalisable solutions, which are often algorithm-based, must be applied.

Reimbursement

Another major consideration is that HTA bodies and payers are investigating novel approaches to reimbursement, including concepts such as coverage with evidence development, cost sharing, and price-volume agreements. As explained in an article in this issue by Michael Köhler and Annette Christoph,¹⁶ (p. 22) early benefit assessment in Germany provides publicly available, comprehensive information – in both scientific

and easily understandable formats – on the added benefit of new drugs.

Given that there is a tendency to rush access to potentially valuable therapeutics and vaccines through Emergency Use Authorizations (EUAs) in the US, and Conditional Marketing Authorizations (CMAs) in the EU, will reimbursement schemes be modified, based on emerging data – which might include a lack of long-term efficacy/safety? The WHO resolution on HTA states that most HTAs should be focused on the domains of safety and effectiveness, and then economic/budgetary areas, with much less emphasis on aspects of ethics, equity, and feasibility.¹⁷

Are there inherent conflicts of interest between regulators and health technology assessors? Do they really share common goals? Is there incentive for cost containment on the part of profit-driven pharmaceutical companies? Historically, commercial approval occurs first, followed by allocation of reimbursement funding. Given the pressures due to urgency, will these two decisions now occur in parallel? If a high-cost therapeutic regimen proves anecdotally effective (à la initial reports regarding hydroxychloroquine and unrestricted use of remdesivir in COVID-19 patients), should the therapy be made available to the public at large? Who should pay for it?

Concluding thoughts

Ultimately, healthcare decisions – whether to approve a drug, device, or vaccine for commercial use or emergency use, and how to cover the costs – rely heavily on human factors. We cannot afford to assess individual cases of need on their situational merits, and therefore, must apply tools that will, by their very nature, be imprecise, imperfect, and uncertain. We cannot avoid influences, whether well-intentioned or malign. All we can do, as both individuals and society, is look after each other and try to ensure that protective ethical standards are in place, unintended consequences are considered, and knowledge is not fixed. It is an evolving process. Ethics DO matter.

Disclaimers

All thoughts and opinions expressed in this article are the author's own.

Conflicts of interest

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Why would the healthcare industry need a doughnut?

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Abstract

Doughnut economics provides a new framework for sustainable development, by balancing the ecological boundaries of the planet with the social boundaries of humanity. The framework provides a valuable opportunity for the healthcare industry to transition to a sustainable way of working – and for policy makers and health technology assessment to drive the healthcare industry towards this future. This article discusses what doughnut economics and the circular economy system can mean for the healthcare industry, policy makers, and health technology assessment, and the role that medical writers and communicators can play in the change to a sustainable future.

Introduction

As global citizens, many of us are becoming increasingly aware of the environmental crisis unfolding around us. Fundamental changes are required across human society for us to thrive as a species. Global economic policy and models are at the heart of the current situation and are central to fixing it, as recognised through the United Nations (UN) 2015 Sustainable Development Goals (SDGs)¹ and the essential ecological changes that are required.² Doughnut economics is a new way of economic thinking that could provide the radical changes needed to tackle the environmental crisis. This article focuses on those elements of this doughnut economics framework that particularly apply to the healthcare industry, health

technology, policy makers, and medical writers and communicators.

What is doughnut economics?

The doughnut economics framework was developed by eminent economist Kate Raworth and is a simple representation of the social and planetary boundaries that underpin human well-being (Figure 1).^{2, 3} The inner ring represents social boundaries, below which no-one should fall; these are the 12 social dimensions derived from the UN SDGs.¹ The outer ring is the ecological ceiling that we must avoid overshooting if we are to live within Earth's life-sustaining systems. The nine planetary dimensions, represented by the outer ring of the doughnut, have been proposed by an international group of Earth-system scientists.²

Currently, we as a species are overshooting nearly all of the planetary boundaries; for

example, global carbon dioxide levels, a control variable for climate change, were nearly 410 parts per million [ppm] in 2019, considerably above the safe upper limit of 350 ppm.^{2,4} Meanwhile, a substantial proportion of the world's population is falling short of the social boundaries. The challenge to 21st century economists, and to all of us, is to bring ourselves inside the doughnut – into the safe and just space for humanity.

The current situation

The prevailing mindset and priorities of governments and businesses alike do not align with the doughnut framework. Endless financial economic growth is a very commonly used target; however, infinite growth is not possible in a system with non-infinite

resources (such as our planet Earth). The primary goal for many businesses is economic growth to satisfy short-term profits and shareholder return rather than improved human prosperity. In addition to linear growth, the linear economy is the norm, which can be described as “take” (energy, materials), “make” (a product), “use” (consume), and “dispose” (leading to waste) (Figure 2). However, this approach is incredibly wasteful of raw materials and finished products.^{2,5} The benefits ecosystems provide in supporting humans have been described as “ecosystem services” (for example, carbon sequestration) and their monetary value has been calculated;⁶ this has highlighted the importance of the natural world on human well-being,

but there is the risk that this approach reduces the living world to a price or asset on a balance sheet in a finance-centric economy.²

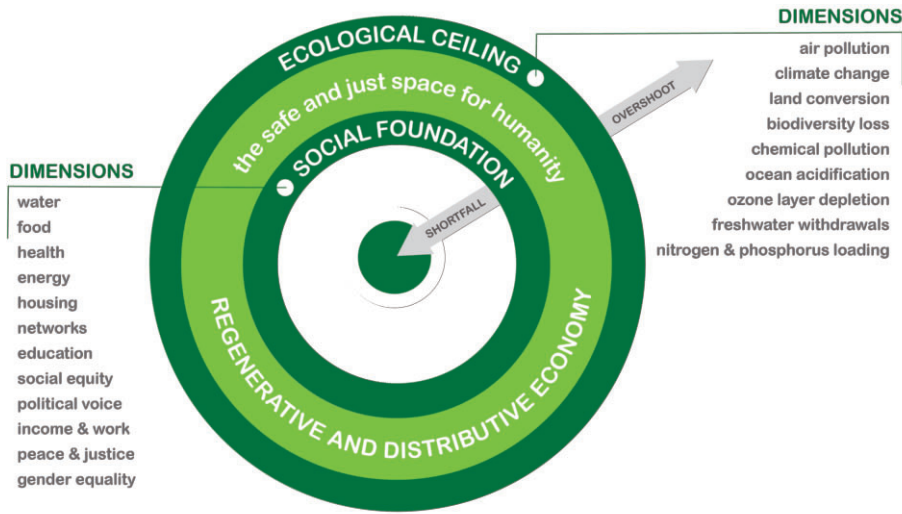
Attitudes and priorities are starting to change. The UN has set out 17 SDGs as a call to action to promote

The circular economy aims to eradicate waste through careful design. The biological or technical components of a product are designed for disassembly and re-purposing with minimal energy, with high-quality resultant products.



A doughnut economy for the healthcare industry

The doughnut represents the social and ecological boundaries that underpin human well-being.



Humans are currently overshooting nearly all of the planetary boundaries, while a part of the world's population is falling short of the social foundation. The challenge is to bring ourselves into the safe and just space for humanity that lies inside the doughnut.

What can the healthcare industry do?

Adapt your business to a circular economy



Reprocess and recycle medical instruments.



Promote reprocessing of single-use devices.



Don't sell a product, sell the service to repair it.



Move your business from money to people-centred.



What can medical writers and medical communicators do?



Use energy from renewable sources and measure your office's carbon and social footprint.



Adapt regulatory documents to The European Green Deal's guidelines.



THE GLOBAL GOALS

Align the company's goals to the UN's Sustainable Development Goals.



Apply the principles of regenerative, circular design to your use of resources and to how your business is run.

Figure 1. The doughnut economics framework: the aim is to exist within the doughnut so that human activity does not go through the ecological ceiling and also ensures that no one is falling short of the social foundation.²

Our work as medical writers and communicators could directly help reduce the shortfall in the social dimensions of "health" and "education", and improvements to one ecological or social dimension can positively impact the others.

"File:Doughnut (economic model).jpg" by DoughnutEconomics is licensed with CC BY-SA 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by-sa/4.0>

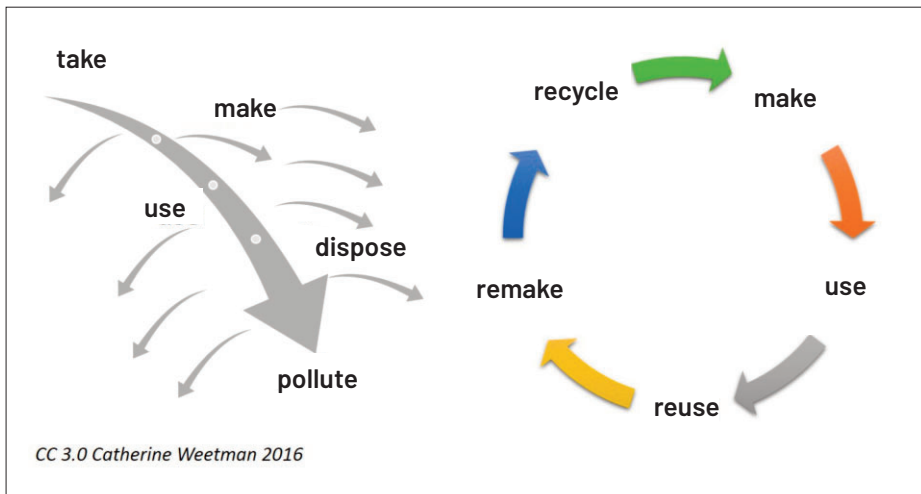


Figure 2. The healthcare industry needs to move from a linear economy (left) to a circular economy (right) to move to the centre of the doughnut.

"File:Linear versus circular.jpg" by Catherine Weetman is licensed with CC BY-SA 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by-sa/4.0>

prosperity while protecting the planet, and the doughnut economics framework was instrumental in the negotiations behind the development of these goals.^{1,2} The European Green Deal is a roadmap towards sustainability; it draws on elements of the doughnut framework and seeks to integrate the UN SDGs.⁷ This has been detailed in a recent article in *Medical Writing*.⁸ Moreover, a wide range of organisations and societies are already engaging with doughnut economics. Two visionary architects recently won the prestigious Pritzker Architecture Prize through their work regenerating buildings rather

than destroying and rebuilding them,⁹ corporate businesses in clothing and retail are rethinking their corporate strategies in line with the doughnut framework,² and cities such as Amsterdam are striving to bring themselves within the doughnut by protecting the environment and natural resources, reducing social exclusion, and guaranteeing good living standards for all.¹⁰

The doughnut, the circular economy, and business

Current, degenerative, linear practices need to

change to ones that are regenerative by design, i.e. restore and renew life cycles. A system central to this is the circular economy, which provides an alternative to the linear economy (Figure 2). This system has the potential to positively impact multiple boundaries in the doughnut framework, both directly (such as reducing pollution and freshwater withdrawals) and indirectly through knock-on effects in other ecological and social dimensions (for example, reducing air pollution leads to healthier living conditions).

The circular economy aims to eradicate waste through careful design. The biological or technical components of a product are designed for disassembly and re-purposing with minimal energy, with high-quality resultant products. Systems are run on renewable energy, and the waste product actually provides a raw material for a new process or product.⁵ Ideally, materials are reused in perpetuity.⁵ The European Union published its Circular Economy Action Plan in 2015,¹¹ which is a key component of the European Green Deal.⁸ Currently, European policies are somewhat conservative and focus on the technical elements of the circular economy rather than taking a more holistic and wide-reaching view, for example aiming to reduce litter rather than tackling the wider issue of over-consumption and materialism.¹² However, as the circular economy gains more traction, policies could become wider in scope and ambition.

Through her experiences with multiple business leaders, Kate Raworth outlines five corporate levels for stepping inside the doughnut



Figure 3. Corporate target levels for sustainability and business responses to the awareness of Earth's planetary boundaries.² Many healthcare industries have Level 4 as a target but should really aim for Level 5.

(Figure 3).² Some of these are probably familiar to us when we hear companies' proclaimed sustainability goals. Figure 3 shows us that many such goals – for example, carbon-neutrality – in fact can go further. The ultimate solution to entering the doughnut is regenerative design, by reconnecting and giving back as much as possible to the natural world that sustains us – making the world a better place than we found it.² One initiative to help businesses achieve regenerative design is biomimicry, which looks to nature's systems to create more sustainable designs and products, from biodegradable detergents to factories that function like a forest.¹³ In addition, the Doughnut Economics Action Lab (DEAL) works with businesses, governments, and communities worldwide to turn doughnut economics into action, via, for example, policy making, reframing economic narratives, and systemic transformation.¹⁴ Also, a prediction tool, the EN-ROADS climate simulator, is being used by organisations to design scenarios to limit future global warming.¹⁵

Doughnut economics and the healthcare industry

The move away from financial gain to human prosperity illustrated by doughnut economics should resonate particularly strongly with the healthcare industry. The European Green Deal sets out a roadmap for greener practices in the healthcare industry.⁸ The pharmaceutical industry is slowly moving towards environmental sustainability; drives towards green materials and cleaner production are showing progress, although other issues such as waste management currently lag behind.¹⁶ In addition, many pharmaceutical companies are setting environmental and sustainability goals such as carbon neutrality and water use reductions,¹⁷ although as discussed above, targets could be more ambitious; for example, a company could strive to become carbon-negative (i.e. removing carbon dioxide from the atmosphere rather than adding it).

A key challenge for healthcare business is changing the ambitions at the very heart of business models towards regenerative design. This means moving away from entrenched

thinking about financial targets and the linear degenerative design, towards assets centred around people and knowledge.² Financial partners, such as investors, are a key part of business. Regenerative enterprises need to move away from the old shareholder-prioritised short-term profit and growth-based dividends model, to longer-term investments with a fair financial return.² One example of such initiatives is paying a share of the income stream to investors in perpetuity instead of profit-related dividends.¹⁸

The circular healthcare economy system could be a valuable opportunity for the healthcare industry to step towards the doughnut economic framework. This system is based on the circular economy design and has been applied to reprocessing and recycling of medical and pharmaceutical devices and instruments. The move away from single-use materials is attractive both environmentally and financially. The COVID-19 pandemic has highlighted supply chain vulnerabilities of single-use equipment,¹⁹ evidenced by shortages in single-use personal protective equipment resulting in their reuse.²⁰ In fact,

many single-use products can be designed for reuse. Steel surgical instruments can be sterilised and reprocessed; non-infectious waste can be recycled, and endoscopes or blood-pressure cuffs can be disinfected for reuse.²¹ Even devices that can only be single-use on safety grounds (needles, catheters) could be recycled to recover the base materials.¹⁹ Many hospitals are already reusing products designated as single-use to decrease costs, and some manufacturers are starting to move towards this model.^{21,22} Furthermore, medical device manufacturers could shift away from selling a product to instead selling a service, where medical equipment is maintained rather than replaced, such as refurbishment of imaging equipment or sharpening of blades.²¹ This encourages manufacturers to design reparability into their products.¹⁹ In fact, moving to a service model could help companies expand their markets by reducing up-front costs¹⁹ and help businesses achieve both ecological and economic balance.

Health technology assessment (HTA) and policy makers are ideally placed to facilitate the drive towards a more regenerative, circular healthcare economy. HTA provides information that inform about the best use of health resources from a societal perspective,²³ which corresponds with the social dimensions of the doughnut framework. Furthermore, environmental impact is already recognised as the unintended as well as the intended consequences of a health technology.²⁴ In addition, frameworks exist for incorporating environmental impacts into an HTA.²⁴⁻²⁶ One of the remits of HTA is to support innovation and help implement new technologies,²³ so HTA can facilitate a shift towards a regenerative, circular economy system, where we can “do more good”, rather than merely “do less harm”.

When considering patient risk, regulatory bodies and professional societies tend to lean towards favouring single-use medical devices for the safety of the individual patient (e.g. minimising risk of infection). If we expand our

The move away from financial gain to human prosperity illustrated by doughnut economics should resonate particularly strongly with the healthcare industry.

The pharmaceutical industry is slowly moving towards environmental sustainability, drives towards green materials and cleaner production are showing progress, but other issues such as waste management currently lag behind.



concept of patient safety to population health, the social and environmental damages and pollution associated with the single-use supply chain must be taken into account, and single-use medical devices do not appear so attractive.¹⁹ Regulation and oversight should promote population health as well as individual patient health and prioritise circular product design and reuse where safe to do so,¹⁹ with single-use labelling only for those products for which safe reuse cannot be achieved.¹⁹

Doughnut economics, medical writers, and medical communicators

What part do medical writers and communicators play in the changing landscape in the light of doughnut economics? First, it is important that we are cognisant of the initiatives driving sustainability. The European Green Deal underlies policies in the healthcare, pharmaceutical, and medical technology sectors, and we need to be aware of how these will be reflected in changes to regulatory documents, such as environmental risk assessment and changes to European grant applications.⁸ As circular design of medical/pharmaceutical devices gains momentum, regulators and policy makers may bring in new legislation to align with circular design. This could affect the way medical device manufacturers operate and the nature of their products – we need to be mindful of such changes. Global value dossiers and messages provide scientific information demonstrating the value of a new product; in the future, these may include environmental or other sustainability information in addition to the effectiveness and safety of a product, which writers may be called on to communicate; therefore, writers need to understand the rationale behind the inclusion of such information in product development and use.

Waste reduction is a key element of the circular economy. This includes research waste, where valuable resources are wasted in unnecessary or poorly designed, conducted, or analysed research studies.²⁷ Medical writers have an important role in reducing research waste, for example by advocating appropriate publication and dissemination of research to interested stakeholders, and adherence to reporting guidelines.

Waste reduction is a key element of the circular economy... Medical writers have an important role in reducing research waste, for example by advocating appropriate publication and dissemination of research to interested stakeholders, and adherence to reporting guidelines.

Table 1. Additional information on doughnut economics

Detailed explanation on doughnut economics	Raworth, K., <i>Doughnut economics: seven ways to think like a 21st-Century economist</i> . 2017, London, UK: Random House.
TED talk by Kate Raworth on doughnut economics	https://www.youtube.com/watch?v=Rhrcbcg8HBw
DEAL – explanation of doughnut economics; tools and guidance on implementing doughnut economics	https://doughnuteconomics.org/
UN Sustainability Development	https://www.un.org/sustainabledevelopment/sustainable-development-goals/
Goals European Green Deal	https://ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en
Detailed explanation on the circular economy	Webster, K., <i>The circular economy: a wealth of flows</i> . 2nd ed. 2016, Isle of Wight, UK: Ellen MacArthur Foundation.

DEAL, Doughnut Economics Action Lab

ination of medical research to interested stakeholders,²⁸ adherence to reporting guidelines,²⁹ and ensuring that systematic reviews have well-designed protocols.²⁷

As business employees (or freelancers) ourselves, it is important we keep our own house in order. We can take action to move our businesses into the doughnut, through educating ourselves on, and if necessary challenging, our companies' carbon and sociological footprints and targets, and strategic direction. For example, EMWA is currently investigating its own ecological footprint with the aim of reducing carbon emissions, as well as looking into the possibility of aligning with the UN SDGs. We can apply the principles of doughnut economics across many aspects of business, through, for example, our pensions (e.g. Environmental, Social and Governance schemes)³¹ and resource use (using renewable electricity, reducing energy wastage, recycling and avoiding single-use crockery and plastic packaging at business lunches).

Our relationships with our clients can build

in elements of the doughnut economics framework and circular economy. Clients may well have sustainability targets they have to meet – we can support these targets with our clients.³² The COVID-19 pandemic has shown us that well-run virtual meetings can offer convenience and free up travelling time, plus deliver huge gains in reducing our carbon footprint. In fact, attendance at one in-person congress can account for around a third of a UK resident's annual carbon emissions, compared with only 0.2% for virtual congresses.³³ We can support clients in advocating virtual meetings as a viable alternative to face-to-face meetings in the right circumstances, whilst also being mindful of peoples' needs for networking and collaboration opportunities that would previously happen at face-to-face meetings. Physical materials, such as those for exhibition booths, can be designed to be reused, repurposed, or at the very least, recyclable, to reduce waste along the regenerative, circular economy principles.

Conclusions

It is becoming increasingly recognised that radical action is required if we are to continue to prosper, or even survive, as a species within a flourishing web of life. We can play our parts as medical writers and communicators and learn from the principles of doughnut economics to



work with our clients and teams to build sustainability into our working lives. It is of course beyond the scope of this article to cover the full story and far-reaching implications of doughnut economics, and further reading is highly recommended (Table 1).

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Conflicts of interest

None to declare.

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Master protocol studies: Embracing the “new normal”

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Abstract

In a post-pandemic world, master protocol studies will be an integral part of the “new normal” for clinical research and play an important role in providing actionable data to support health policy and resource allocation. Medical writers and study teams alike will be expected to be fluent in the development of clear and coherent protocols to support these studies. Here we provide a brief orientation on master protocol study designs, protocol structures, and methods to support medical writers through the protocol development process.

Introduction

The emergence of COVID-19 has had a considerable global impact, including extensive disruption to ongoing clinical research and patient care.¹ In response, the global research community embarked on thousands of clinical studies to not only understand disease pathology but also identify safe and efficacious treatments. As researchers and patients engaged in this process, the absence of a coordinated response and the ensuing fragmented approaches impeded health policy decision-making and appropriate resource allocation.

Current estimates suggest that only 6% of COVID-19 clinical studies in the US are expected to yield actionable data to support decision-making.² The primary barriers for achieving actionable data were poor enrolment due to overlapping and competing studies for similar patient populations, and studies conducted without the robustness needed for regulatory approval.^{2,3} However, during the pandemic, master protocol study designs have been shown



to be a more structured and sustainable approach to clinical study evaluation.⁴ By adopting a master protocol study design, enhanced efficiency and uniformity (by standardising study design and

operation procedures) facilitate the parallel development and parallel evaluation of multiple interventions.^{3,4}

From a historical perspective, the origins and

early use of master protocol studies in oncology targeted prevalent biomarkers and genetic subtyping to address multiple clinical questions within the same overall study structure. Until recently, the use of master protocol studies has steadily increased and branched out into other therapeutic areas; examples include Alzheimer’s disease (DIAN-TU), Ebola (PREVAIL II), and community acquired pneumonia (REMAP-CAP). Then, in early 2020, COVID-19 accelerated the adoption trajectory of master protocol studies as governments and researchers established far-reaching master protocol studies to address the public health crisis. While the list of studies is long, notable contributions include: the World Health Organization’s Solidarity Trial – a master protocol study to investigate repurposed antiviral drugs for COVID-19; ACTIV network – the US National Institutes of Health’s (NIH) four fast-track focus areas for the treatment of COVID-19; ANTICOV – the largest COVID-19 study

During the pandemic, master protocol study designs have been shown to be a more structured and sustainable approach to clinical study evaluation.

conducted in Africa; and RECOVERY – the UK platform study that received international recognition for demonstrating dexamethasone and tocilizumab improved survival of hospitalised COVID-19 patients.^{4–9}

Defining a master protocol study – in all but name

Clear definition and classification of **master protocol studies** remains a key challenge that has obstructed widespread adoption of such designs. Although key opinion leaders and regulators agree that master protocol studies are characterised by multiple parallel substudies that share a common overarching framework, how these studies are defined and categorised has not yet reached maturity. Definitions of a master protocol study from the United States Food and Drug Administration (FDA), the European Economic Area Heads of Medicines Agencies (HMA) Clinical Trials Facilitation and Coordination Group

(CTFG), and EU Patient-centric clinical trial Platforms (EU-PEARL) show a continuing evolution in understanding, with the most comprehensive description recognised by EU-PEARL (Table 1).^{10–15}

In relation to the protocol document itself, terminology is equally evolving, with only the CTFG and EU-PEARL providing descriptions for master protocol content and platform study content, respectively.^{12,13} In order to differentiate between the master protocol study design and the protocol document content, we propose the use of **core protocol vs subprotocol** descriptors for common and substudy-specific content, respectively.

The seminal work by Woodcock and LaVange from the US FDA provided the initial classification of master protocol studies as **basket, umbrella, or platform** designs (Table 2).^{10,11} Real-world application of these definitions suggests that the initial classification was incomplete, with only 57% of studies included in a recent systematic review being correctly classified.¹⁶ More recently, EU-PEARL further expanded the definitions to include a **matrix** design and a **multi-arm multi-stage (MAMS)** analysis framework.

Table 1. Terminology

Definition	Description	Reference
Master protocol study	A single overarching design developed to evaluate multiple hypotheses , and the general goals are to improve efficiency and establish uniformity through standardisation of procedures in the development and evaluation of different interventions. Under a common infrastructure, the master protocol may be differentiated into multiple parallel substudies to include standardised study operational structures, patient recruitment and selection, data collection, analysis, and management.	EU-PEARL 2020 Park et al 2019
Protocol scaffold	A visual aid to help plan for how the protocol content will be distributed between the core and subprotocols. A protocol scaffold is most easily presented by extracting the protocol template’s table of contents and indicating whether content is located in the core vs subprotocols, whether content is repeated, or whether content is complementary.	N/A
Core protocol (document)	Protocol document describing content for the overarching study design that is applicable to all substudies. Common content examples include: a general introduction to the master protocol study, common objectives and endpoints/estimands, rationale for conducting the master protocol study, and common administrative, regulatory, and operational elements. Also referred to as “master protocol”.	N/A
Subprotocol (document)	Protocol document or content that is specific to an individual substudy. Synonyms include: “intervention specific appendices”, “domain specific appendices”, “study modules” and “comparison protocols”.	N/A

Abbreviation: EU-PEARL, EU Patient-centric clinical trial Platforms

In essence, master protocol studies that are designed with a fixed number of populations and/or interventions can be categorised as a basket (single intervention, multiple populations), umbrella (multiple interventions, single population), or matrix (multiple interventions, multiple populations) study. If the study is designed with the ability to prospectively add or stop substudies, the study is categorised as a platform study.

Clinical study protocol structure – choosing the right fit

An overly complex study protocol can have long lasting and potentially devastating results on a study. An overly burdensome protocol can lead to study sites redirecting participants to other more preferable studies and participant dropout rates in excess of 30%.¹⁷ The body of guidance for conducting master protocol studies has focused

An overly burdensome protocol can lead to study sites redirecting participants to other, more preferable, studies and participant dropout rates in excess of 30%.

on the operational implementation of the study protocol; yet, little credence has been given to the protocol structure – a process that makes decisive contributions to how multiple substudies are submitted, updated and reported. In 2015, Hollingsworth recognised the need to introduce flexibility into the protocol’s structure to accommodate master protocol study designs.¹⁸ In the years since Hollingsworth’s publication, adoption of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations and the TransCelerate Biopharma Common Protocol Template have consolidated industry protocols around a common framework that is more amenable to standardised document structures for master protocol study designs.^{19,20}

The complexity and variability in master protocol study design currently precludes a “one

size fits all” approach. The protocol structure chosen will need to balance the study needs against the resultant trade-offs, a decision process that can impact study conduct and data integrity if done poorly. In the most simplistic structural interpretation, where the subprotocol content is minimal, a standard protocol structure would be most appropriate. However, this approach can soon become complex and difficult to understand as more content is added. Appendix/annex and independent subprotocol structures offer comparative clarity for larger studies with more substudies, as well as studies with few substudies of substantial subprotocol content. In addition, independent subprotocol structure offers additional flexibility when recurrent or parallel amendments are anticipated throughout the life of the study. A review of the current literature does not indicate preferred structures for the protocol document by study design; nevertheless, field experience from the STAMPEDE and FOCUS4 platform studies support appendix/annex or independent subprotocol structures for platform studies.²¹

Table 2. Classification of master protocol studies

Name	Description	Reference
Basket	A study designed to test a single intervention in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics	Woodcock & LaVange 2017 FDA 2018
Umbrella	A study designed to evaluate multiple interventions administered as single drugs or as drug combinations in a single disease population .	Woodcock & LaVange 2017 FDA 2018
Platform	A study designed to evaluate multiple interventions in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm.	Woodcock & LaVange 2017
Matrix	A study that is both an umbrella study and a basket study , including analyses in multiple disease subtypes. Many platform studies are matrix studies with the additional feature that as the study progresses and interventions leave the study, new interventions may enter, and the study does not have an initially fixed duration or sample size.	EU-PEARL 2020
Multi-Arm Multi-Stage (MAMS)	An analysis framework that can be used in combination with Umbrella or Platform master protocol study designs. This framework analyses study results in a Group Sequential framework and controls overall Type-1 Error and is attractive for studies intended for regulatory submission. This framework avoids features that are more problematic for regulatory submission such as response adaptive randomisation, sub-group analysis, and Longitudinal Modelling.	EU-PEARL 2020

Abbreviations: EU-PEARL, EU Patient-centric clinical pLatforms; FDA, Food and Drug Administration

Table 3. Protocol structure

Protocol structure	Description & structure example	Benefits	Risks
Integrated subprotocols	<p>Description: Substudy protocol content is integrated within the core protocol structure</p> <p>Structure example: Section 5: Study Population 5.1: Inclusion Criteria (IC) 5.1.1: IC for Substudy 1 5.1.2: IC for Substudy 2 5.2: Exclusion Criteria (EC) 5.2.1: EC for Substudy 1 5.2.2: EC for Substudy 2</p>	<ul style="list-style-type: none"> ● Easy to implement ● Maintains standard protocol structure ● Reduced structural complexity (compared to other structures below) ● Minimal impact to protocol development processes and timelines ● Single document for future amendments 	<ul style="list-style-type: none"> ● Comprehension reduced with increasing substudy content ● Can substantially increase the length of the standard protocol structure if there are numerous substudies ● No single location for substudy information, requires detailed review and comprehension of the protocol for all study staff ● Difficult to amend if new substudies are required
Appendix/Annex subprotocols	<p>Description: Substudies are provided as separate appendices/annexes to the core protocol</p> <p>Appendix Structure example: Core protocol Appendices 1-9 Appendix 10: Subprotocol 1 Appendix 11: Subprotocol 2</p> <p>Annex Structure example: Core protocol with appendices 1-9 Annex Document 1: Subprotocol 1 Annex Document 2: Subprotocol 2 (Annex documents submitted under the same submission number)</p>	<ul style="list-style-type: none"> ● Clearer comprehension when there are multiple subprotocols with substantial content ● Maintains standard protocol structure ● Clear division for subprotocol information (useful when not all sites are enrolling across all subprotocols) ● Easy to amend if new substudies are required ● Single document for future amendments 	<ul style="list-style-type: none"> ● Redundant if substudy information is brief and/or there are few substudies planned ● Reduced flexibility for amendments with increasing number of substudies as substudies cannot be independently updated (amendments would be queued, e.g., subprotocol 2 could not be amended while subprotocol 1 was undergoing an amendment) ● Risk of repetition, redundancy, or conflicting statements in subprotocols compared to the core protocol if not managed correctly ● Moderate impact to protocol development processes and timelines ● Increased reporting complexity as a single study report is required ● Increased study disclosure complexity as all substudies need to be summarised and submitted simultaneously
Independent subprotocols	<p>Description: Substudies are provided as independent subprotocol documents and registered separately</p> <p>Structure example: Core protocol (submitted alongside subprotocol 1 and subprotocol 2) Subprotocol 1: EudraCT number: 2021-xxxxxx-01 Subprotocol 2: EudraCT number: 2021-xxxxxx-02</p>	<ul style="list-style-type: none"> ● Clearer comprehension for multiple subprotocols with substantial content AND where the core protocol information is limited to summary operational details (most common for platform and matrix studies) ● Maintains standard protocol structure ● Clear division for subprotocol information (useful when not all sites are enrolling across all subprotocols) ● Easy to amend if new substudies are required ● Subprotocols can be amended independently and submitted in parallel (if desired) ● Independent reporting of each substudy ● Study disclosure is less complex than summarising all substudies together 	<ul style="list-style-type: none"> ● Redundant if core protocol contains most of the content (appendix/annex substudies preferable) ● Core protocol updates impact multiple submissions that need to be updated in parallel ● Risk of repetition, redundancy, or conflicting statements in subprotocols compared to the core protocol if not managed correctly ● High impact to protocol development processes and timelines – more upfront planning and time requirements from team members ● Increased administrative burden if multiple amendments are conducted in parallel

An additional consideration for the protocol structure is the regulatory requirements of the study. There are limited submission guidelines available as only the FDA and the CTFG have released guidance on master protocol studies.^{11,12} Both recommend two submission structures: either a single submission with multiple substudy protocols under a single EudraCT/NCT number (integrated sub-protocols or appendix/annex subprotocols) or independent subprotocols, each accompanied by the common master protocol, submitted under individual EudraCT/NCT numbers. The submission strategy (integrated or appendix/annex vs independent subprotocols) will depend on the operational needs and long-term considerations for the overall master protocol study.

Directing protocol development – flexibility is key

Identifying the protocol development team

Although often not the responsibility of the medical writer, confirming study team members prior to protocol development is an important task to start gravitating individual expertise around the collective objective(s) of the study. This process can be challenging, in particular for study teams that are managing their first master protocol study. Unlike traditional study protocols, identifying all team members prior to protocol development may not be straightforward since the team structure is dependent on the overall ambition of the study design, number of interventions, patient populations, and countries involved. Examples for each have been provided below:

- **Study design:** The study design may include adaptive elements, decentralised components, or digital health technologies. Early engagement with the relevant expertise will minimise the risk of substantial changes late in the protocol’s development.
- **Multiple interventions/participant populations:** Depending on the organisation(s) involved, there may be multiple representatives for the same function. For example, a master protocol study that wishes to include multiple interventions may require representation from each of the intervention groups – such as medical professionals or study/programme leaders. Equally, a study with multiple participant populations will require adequate representation for each population to ensure the suitability and applicability of the study design.



- **Geographic footprint:** Like all multiregional studies, regulatory requirements for countries in which the study will be conducted may influence the protocol. Master protocol studies may require additional discussion and engagement with regulatory agencies or regulatory professionals during the protocol’s development.

Agreeing on the protocol structure

Ensuring all team members are aware of, and agree on, the protocol structure prior to initiating protocol development will reduce the risk that conflicting opinions on protocol structure arise (due to either unfamiliarity with the master protocol study designs, in general, or the particular study requirements) that may extend

review cycles or require additional document drafts. Both can damage the team’s decision-making ability and reduce overall team efficiency that, in turn, may not only extend development time but also reduce overall quality.

To support this task, the medical writer can initiate early discussions to identify the most suitable protocol structure. Points to consider/questions to ask:

- **Does the master protocol structure give optimal clarity and coherency for readers?** A common challenge for all protocol writing is the multidisciplinary audience with variable clinical experience and study involvement. Master protocol studies have audiences that may also engage with the content differently – not as a whole single study, but rather as separate individual substudies. This means that although two readers may be reading the same protocol document, each may be approaching the content with differing participant populations, interventions, or study schedules in mind. Therefore, does the chosen structure facilitate readers being able to identify relevant substudies easily?
- **Will information be repeated, or will a single source of information be cross-referenced throughout?** There is a strong argument for cross-referencing a single source rather than repeating information within or across the core and/or subprotocols – in that duplication breeds inconsistency – although this view is not shared by all. If the preference is to repeat information across multiple sections, it is important to clarify what essential content needs repeating (e.g., overarching objectives and endpoints, or eligibility criteria), how team members will comment on multiple repetitions of the same content, and how this will be controlled for consistency.
- **What information will be specific to the core protocol vs subprotocol?** What information will be applicable across all substudies and what will be specific to each substudy? For example, will each substudy follow the same schedule of assessments? Will there be a core set of eligibility criteria with additional criteria for each substudy?

After the provisional decision of the protocol structure has been made, the medical writer may wish to develop a **protocol scaffold** to aid the team’s understanding of what the protocol

structure will look like (Table 1). By using a simple tool to visualise the content distribution, the medical writer can minimise the risk of the study team rejecting the protocol structure during the team’s revision and thus, requiring substantial changes midway through the protocol’s development.

Establishing (and maintaining) timelines

In combination with agreeing on a protocol structure and protocol scaffold, upfront agreement on timelines is an important step in aligning expectations while allowing for sufficient protocol development time. We propose two approaches:

1. A **parallel approach** that follows a similar approach to standard protocol development (all content is developed together) with additional time included for content development and review.
2. A **staggered approach**: leading content (such as the core protocol) is submitted for review first, and then trailing content (such as the subprotocols) is submitted once the initial content has been reviewed.

Points to consider/questions to ask:

- **What approach should be followed?** In certain circumstances a parallel approach would be preferable e.g., where several indications are involved, and it is beneficial to engage all team members at the same time. By contrast, a smaller study team covering all substudies would likely benefit from reviewing in a staggered manner as this would mitigate reviewers being overburdened by the review requirements.
- **Parallel approach**: How long will the timelines be extended to account for the additional content to be reviewed while maintaining consistency? Will all team members need to complete the review within the timeframe, or will it only be key team members (i.e., will this approach fit all team members)?
- **Staggered approach**: What content should be leading and what content should be trailing? Will the team members be engaged and able to accommodate the review requirements over the whole review period

(i.e., are there any planned absences or work requirements that would interfere)? Will there be any periods where all content needs to be reviewed together (e.g., when the protocol is close to being finalised)?

Conclusions

Master protocol studies are highly complex. The complexity and variability in the accompanying protocol development process can test even the most experienced medical writer and study team. Standard protocol templates and approaches are often inadequate for addressing the complexity and multiple configurations of a master protocol study. We hope the guidance

provided herein will be of use in the development of clear and coherent protocols to support master protocol studies.

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Disclaimers

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

Conflicts of Interest

The authors declare no conflicts of interest.

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Launch of "EMA medical terms simplifier" for medical terms used by EMA

March 19, 2021

Medical writers at EMA have published an "EMA medical terms simplifier" (https://www.ema.europa.eu/en/documents/other/ema-medical-terms-simplifier_en.pdf) on the "Glossaries" page of EMA's website (under "About us") to provide public-friendly descriptions of medical terms used for side effects of medicines and mechanisms of action. These descriptions are used daily to prepare EMA materials that are shared with the public.

The medical terms simplifier focuses on side effects and other terms used in medicines information and assessments of medicines. It does not cover rarely used terms, most disease

states, very specialised areas, or the broader field of medical science.

The "EMA medical terms simplifier" has been assembled over many years by EMA medical writers who use these plain-language descriptions to prepare public-friendly communications. Having become increasingly aware that there was no single resource for describing common medical terms found in medicines information, the team worked to produce a public-domain version of this resource.



This resource may be of value to external stakeholders and partner organisations involved in communicating with the public. EMA medical writers will continue to maintain and further develop this resource over time.

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Success rate for marketing authorisation applications from SMEs doubles between 2016 and 2020

June 28, 2021

EMA has published a report highlighting the Agency's support for micro-, small-, and medium-sized enterprises (SMEs) which develop and market medicines for human or veterinary use in the European Union. The report covers the period from 2016 to 2020.

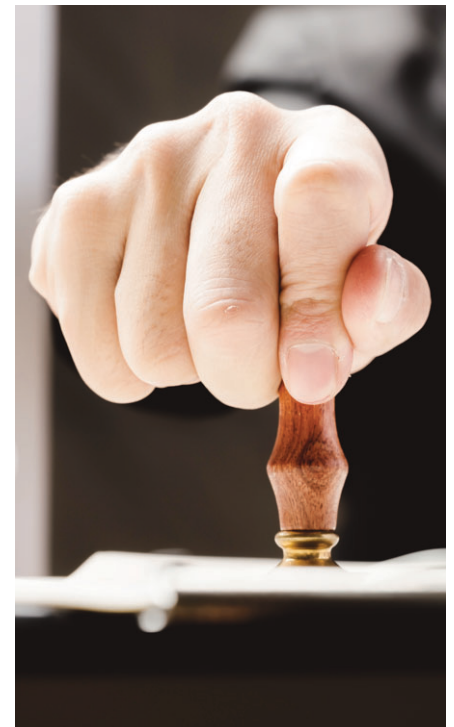
Since 2016, the success rate of marketing authorisation applications for human medicines submitted by SMEs has more than doubled. In 2016, 40% of medicines with an SME applicant received a positive opinion. In 2020, the number had increased to 89%. In 2020 alone, SMEs were behind 16 recommendations for approval of a new medicine, which accounted for almost 20% of all medicines for human use recommended for approval by EMA last year. Half of them targeted rare diseases.

In the veterinary area, 14 medicines received a positive opinion by the Agency in the last 5 years. Almost half of these had received scientific

advice from the Agency. Six out of the 14 were veterinary medicines for minor use / minor species (MUMS).

The report features key facts and figures of companies that are registered as SMEs with EMA. SMEs are a major driver of innovation in the pharmaceutical industry and the Agency provides them with access to a number of incentives, including regulatory assistance from a dedicated SME Office and reduced fees for certain procedures.

The publication of the report marks the 15-year anniversary of the adoption of the SME Regulation that promotes innovation and the development of new medicines in Europe. Since the creation of the SME Office in 2005, more than 130 medicines developed by SMEs have been approved following an EMA recommendation and contribute to public and animal health.



New treatment for rare autoimmune disease of nerve cells

April 23, 2021



Photo: David Matos / Unsplash.com

EMA has recommended granting a marketing authorisation in the EU for Enspryng (satralizumab; from Roche) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adults and adolescents from 12 years of age who are positive for anti-aquaporin-4 antibodies (AQP4-IgG).

NMOSD is a rare and life-threatening condition that most commonly affects the optic nerves and spinal cord. This disorder can lead to reduction or loss of vision, loss of sensation, loss of bowel and bladder control, weakness and

paralysis of the arms and legs. NMOSD is thought to be caused by an abnormal reaction of the immune system that causes damage to healthy nerve cells. It is characterised by relapsing attacks, with symptoms coming back periodically. It is estimated that NMOSD affects approximately 1-2 in 100,000 people in the EU.

Enspryng works by reducing and preventing the attacks caused by NMOSD. Satralizumab, the active substance contained in Enspryng, is an antibody designed to block the inflammatory

effects of interleukin-6 receptor (IL-6), which is involved in the pathogenesis of the NMOSD.

Enspryng will be available as a pre-filled syringe and will be administered as a solution through an injection under the patient's skin (subcutaneously). The first three injections are given 2 weeks apart followed by one injection every 4 weeks. It can be used on its own or in combination with medicines that reduce the activity of the immune system (immunosuppressive therapy).

The opinion of EMA's human medicines committee (CHMP) is mainly based on two randomised clinical studies which involved a total of 184 patients. The clinical studies showed that the chance of a relapse happening in 119 patients who were AQP4+ and received Enspryng alone or in combination with immunosuppressive therapy was a quarter of that in the control group receiving placebo alone or in combination with other immunosuppressive therapy. The most common side effects observed in clinical trials were headache, joint pain, white blood cells count decreased, and reactions at the site of injection.

The opinion adopted by the CHMP is an intermediary step on Enspryng's path to patient access. The 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 or use of this medicine in the context of the national health system of that country.

The June 2022 edition of *Medical Writing*

The implementation date of the EU Medical Device Regulation has arrived, marking a new era of heightened attention to medical device safety and performance. This issue will explore the experiences, challenges, and lessons learned over the last years preparing for the MDR requirements as well as potential opportunities these changes bring. Moreover, we touch base on the implementation of the EU In-Vitro Diagnostic Regulation and on other aspects of writing for medical devices.

Guest Editors: Kelly Goodwin Burri and Beatrix Doerr

Medical devices

Don't miss!

First gene therapy to treat children with rare inherited neurological disease

May 21, 2021

EMA has recommended granting a marketing authorisation in the EU for the gene therapy Skysona (elivaldogene autotemcel; from bluebird bio, Netherlands) for the treatment of children with cerebral adrenoleukodystrophy (CALD), a severe form of a rare inherited neurological disease. This disease, seen almost exclusively in males, affects the brain and leads to an irreversible loss of neurological functions.

CALD is the most common form of adrenoleukodystrophy (ALD), a rare disease affecting approximately 1 in 21,000 newborn males. This condition is caused by abnormalities in a gene called ABCD1 which is responsible for the production of a protein called ALDP (adrenoleukodystrophy protein). Patients with the disease lack ALDP which is needed to break down fatty substances in the body called very long chain fatty acids (VLCFA). As patients with CALD cannot break down these fatty substances, they gradually build up in cells in the brain. The build-up of VLCFA leads to inflammation and destruction of the protective sheath (myelin) that insulates and improves the way the nerves function.

Forty percent of boys diagnosed with ALD develop CALD, typically during childhood. If untreated, nearly half of patients with CALD die within 5 years of symptom onset. Currently, there is no medicine approved for the treatment of this disease. The only therapeutic intervention available to CALD patients is transplantation of

stem cells (cells that can develop into different types of blood cells) from a donor. This procedure presents several potential complications and risks which are reduced for those patients who have a matching sibling donor. However, these represent less than 30% of patients with CALD. Therefore, there is an unmet medical need for these patients.

Skysona is made up of immature bone marrow cells that are taken from the patient. The cells are then modified by a virus – a so-called “lentivirus” that has been changed in order not to cause disease in humans – that contains a functional copy of the gene ABCD1 for the ALDP protein, so that this gene is carried into the cells. When these modified cells are given back into the patient by a drip (infusion) into a vein, they are expected to spread through the body and develop into different types of healthy cells, including brain cells, that produce the ALDP protein that patients with CALD lack. As a result, patients should be able to break down the accumulated VLCFA and this will help to reduce the symptoms of the disease.

Skysona is a one-time treatment which can only be given in a specialised hospital by doctors who are experienced in treating patients with CALD, transplanting bone marrow, and using gene therapy medicines.

EMA’s recommendation for a marketing authorisation is based on evidence from a single-arm clinical trial that enrolled 32 male patients

with CALD aged 17 years or younger. The results from this study were compared to those from a study in which 59 patients had a stem cell transplantation (either from a matched sibling donor or a matched non-sibling donor). All the patients in the main clinical trial were enrolled in a long-term follow-up study.

An analysis conducted after 24 months from the infusion on 30 subjects enrolled in the study concluded that for 27 of them (90%) treatment with Skysona preserved motor function and communication ability and improved survival when compared to untreated patients at an early stage of cerebral disease. The most serious adverse reaction in the clinical trials for Skysona was low levels of all types of blood cells (pancytopenia).

Adding a new gene into the stem cells could theoretically cause blood cancers. This was not seen during the clinical trial but after the treatment, patients will be monitored with blood tests to check for any signs of cancer of the blood. Additional long-term efficacy and safety data are being collected through one ongoing study and a long-term registry. All results must be included in post-marketing safety reports, which are continuously reviewed by EMA.

Skysona was designated as an orphan medicinal product on June 6, 2012. Skysona is indicated for the treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age, with an ABCD1 genetic mutation, and for whom a human leukocyte antigen (HLA) matched sibling haematopoietic stem cell (HSC) donor is not available.



First treatment for rare liver disease

May 21, 2021

EMA has recommended granting a marketing authorisation in the European Union for Bylvay (odevixibat; from Albireo) for the treatment of Progressive Familial Intrahepatic Cholestasis (PFIC) in patients aged 6 months or older. PFIC is a rare, life-threatening liver disease. Patients have liver cells that are less able to secrete bile (a fluid produced in the liver that helps to break down fats). The build-up of bile in liver cells causes liver disease. The symptoms typically develop in infancy, usually in the first months of life. Approximately only half of the children affected by the disease survive beyond the age of 10 years.

Severe itching (pruritus) is common in children diagnosed with PFIC. This can lead to sometimes serious scratching injuries, loss of sleep, irritability, and poor attention. There is a high unmet need for these patients whose treatment options are limited to surgical intervention and off-label symptomatic medical therapies. If untreated, many PFIC patients progress to end-stage liver disease and require liver transplantation.

The active substance of Bylvay is odevixibat, a reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT) that acts locally in the distal ileum (the last part of the small intestine), reducing the reuptake of bile acids and increasing the clearance of bile acids through the colon.

The main study on which the recommendation by EMA's CHMP is based was a double-blind, randomised, placebo-controlled phase 3 study, which investigated the efficacy and safety of Bylvay in children with PFIC. The results showed a significant reduction in serum bile acids accompanied by a significant reduction in pruritus in patients treated with odevixibat. These results were maintained in an ongoing, long-term open-label follow-up study. Hepatic parameters and fibrosis scores were improving or were stable for the duration of the study (max. 72 weeks). However, more data are needed to determine if odevixibat

can delay disease progression and the need for liver transplantation. The CHMP therefore requested a registry-based efficacy study as a follow-up.

The most common side effects are diarrhoea, abdominal pain, haemorrhagic diarrhoea, soft faeces, and hepatomegaly (enlarged liver). No clinically significant differences in the pharmacokinetic, safety and tolerability profile of odevixibat were observed based on age, sex or race.

As PFIC is a very rare disease, the CHMP agreed that it is not possible to provide comprehensive data on the efficacy under normal conditions of use. Therefore, the Committee recommended granting a marketing authorisation under exceptional circumstances and requested the applicant to complete a registry-based study to further characterise the efficacy of Bylvay in patients aged 6 years or older.

A marketing authorisation under exceptional

circumstances allows patients access to medicines that cannot be approved using a standard authorisation route as comprehensive data cannot be obtained, either because there are only very few patients with the disease, the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge. These medicines are subject to specific post-authorisation obligations and monitoring.

Bylvay, was designated as an orphan medicinal product on July 17, 2012, for the treatment of Progressive Familial Intrahepatic Cholestasis. On October 13, 2017, the medicine was accepted in EMA's PRiOrity MEdicines (PRIME) scheme that offers extra support to developers of medicines that have the potential to address patients' unmet medical needs. The CHMP reviewed the application for Bylvay under its accelerated assessment procedure, which allows the speeding up of patients' access to medicines.



First cell-based gene therapy to treat adult patients with multiple myeloma

June 26, 2021

EMA has recommended granting a conditional marketing authorisation in the EU for Abecma (idecabtagene vicleucel; from Celgene Europe BV) for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three previous therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose cancer has worsened since receiving the last treatment.

Multiple myeloma is a rare cancer of a type of white blood cell called plasma cells. Normal plasma cells are found in the bone marrow and are an important part of the immune system. Plasma cells make the antibodies that enable the body to recognise and attack germs such as viruses or bacteria. In multiple myeloma, the

proliferation of plasma cells is out of control, resulting in abnormal, immature plasma cells multiplying and filling up the bone marrow. When plasma cells become cancerous, they no longer protect the body from infections and produce abnormal proteins that can cause problems affecting the kidneys, bones, or blood.

Despite the development and approval of a range of new medicines for the treatment of multiple myeloma over the past few years, there are limited therapeutic options for patients who have already received three major classes of drugs (immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies) and no longer respond to these medicines. Therefore, new medicines are needed for patients whose disease returns after treatment.

Abecma is a genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy and the first cell-based gene therapy to treat adult patients with multiple myeloma. Each dose of Abecma is created by collecting a patient's own T-cells (i.e. white blood cells that help the body fight infections) and genetically modifying them so that they include a new gene that helps the body target and kill the myeloma cells. These modified immune cells are then infused back into the patient's blood.

The main study on which the recommendation for a conditional marketing authorisation is based was a Phase 2, multicentre, open label, single-arm clinical trial. The study investigated the efficacy and safety of Abecma in 140 adult patients with relapsed or refractory multiple myeloma who had received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and who didn't respond to the last treatment regimen. About 67% of patients enrolled in the study responded to the treatment and maintained remission (a period without disease signs or symptoms after treatment) for about 11 months on average. Of those studied, 30% showed complete response (i.e. disappearance of signs of cancer).

The main safety concerns related to the administration of Abecma are cytokine release syndrome (CRS) (i.e. a condition causing fever, vomiting, shortness of breath, headache, and low blood pressure), neurological toxicity, cytopenias (i.e. low number of cells in the blood) and infections, which can be life-threatening.

Additional efficacy and safety data are being collected through the submission of follow-up data from the main clinical trial and through an ongoing study that will compare the efficacy and safety of the medicine with standard triplet regimens in patients with relapsed and refractory multiple myeloma.

Abecma was designated as an orphan medicinal product on April 20, 2017. Following this positive CHMP opinion, the Committee for Orphan Medicinal Products (COMP) will assess whether the orphan designation should be maintained.

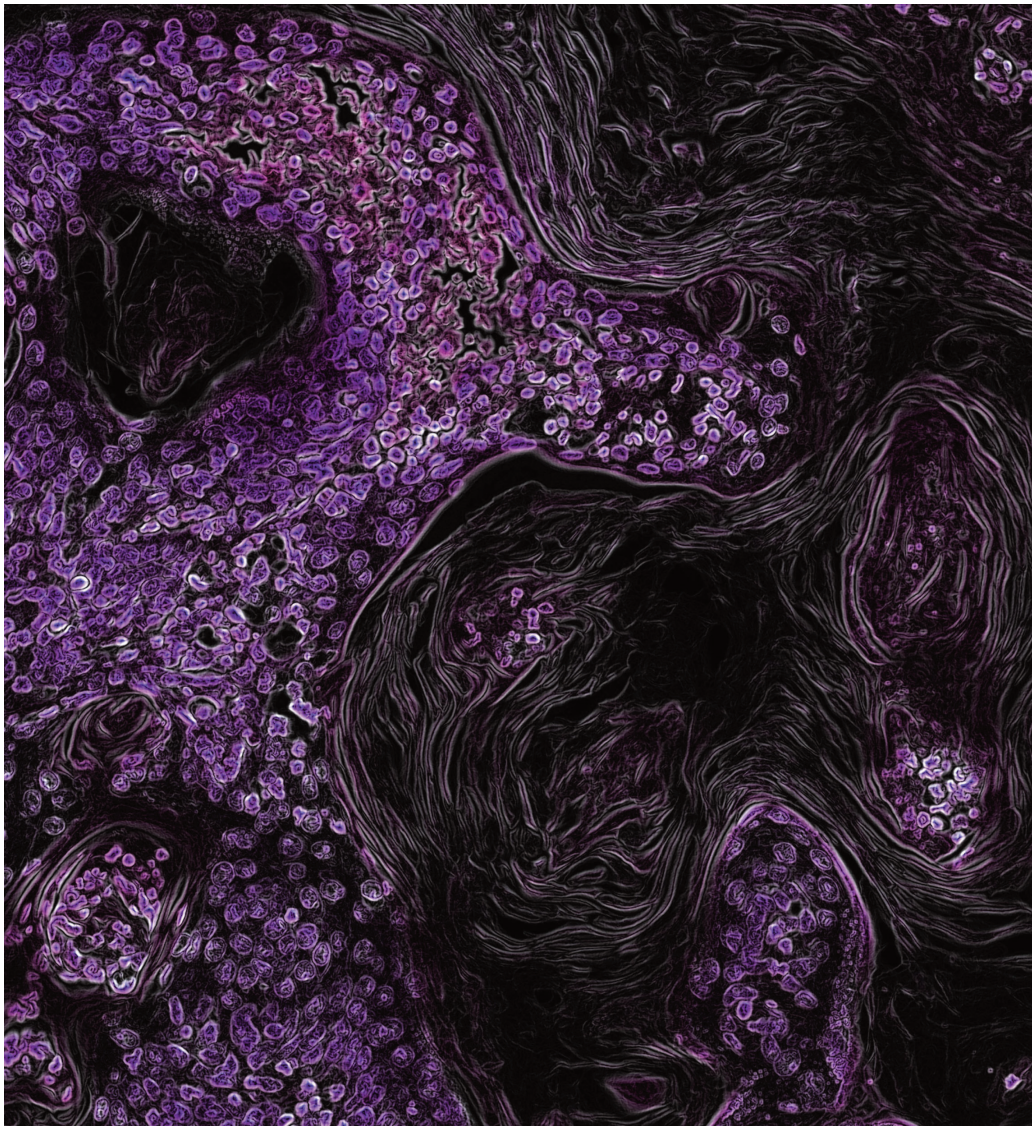


Photo: Eric Snyder / Unsplash.com

Use of antibiotics in animals is decreasing

June 30, 2021

Use of antibiotics has decreased and is now lower in food-producing animals than in humans, says the latest report published by the European Food Safety Authority (EFSA), the EMA, and the European Centre for Disease Prevention and Control (ECDC).

Making a One Health approach, the report from the three EU agencies presents data on antibiotic consumption and development of antimicrobial resistance (AMR) in Europe for 2016–2018. AMR is a significant global public health problem that represents a serious economic burden.

The significant fall in antibiotic use in food-producing animals suggests that the measures taken at country level to reduce use are proving to be effective. Use of a class of

antibiotics called polymyxins, which includes colistin, nearly halved between 2016 and 2018 in food-producing animals. This is a positive development, as polymyxins are also used in hospitals to treat patients infected with multidrug-resistant bacteria.

The picture in the EU is diverse – the situation varies significantly by country and by antibiotic class. For example, aminopenicillins, 3rd- and 4th-generation cephalosporins and quinolones (fluoroquinolones and other quinolones) are used more in humans than in food-producing animals, while polymyxins (colistin) and tetracyclines are used more in food-producing animals than in humans.

The report shows that the use of carbapenems, 3rd- and 4th-generation

cephalosporins and quinolones in humans is associated with resistance to these antibiotics in *Escherichia coli* infections in humans. Similar associations were found for food-producing animals.

The report also identifies links between antimicrobial consumption in animals and AMR in bacteria from food-producing animals, which in turn is associated with AMR in bacteria from humans. An example of this is *Campylobacter* spp. bacteria, which are found in food producing animals and cause foodborne infections in humans. Experts found an association between resistance in these bacteria in animals and resistance in the same bacteria in humans. The results presented in this report call for continued efforts to tackle AMR at national, EU, and global level across the healthcare sectors.



Photo: David Dolenc / Unsplash.com

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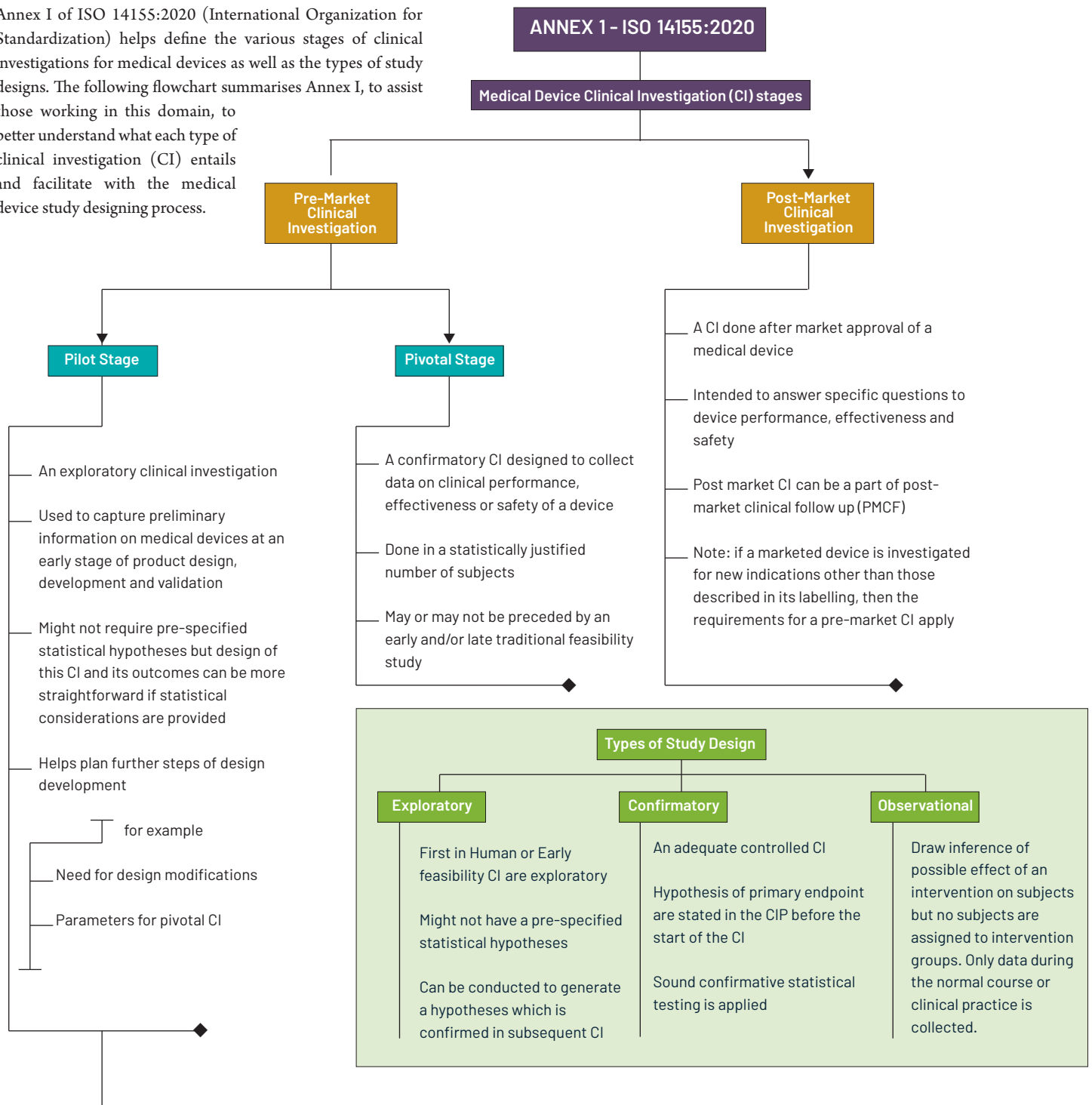
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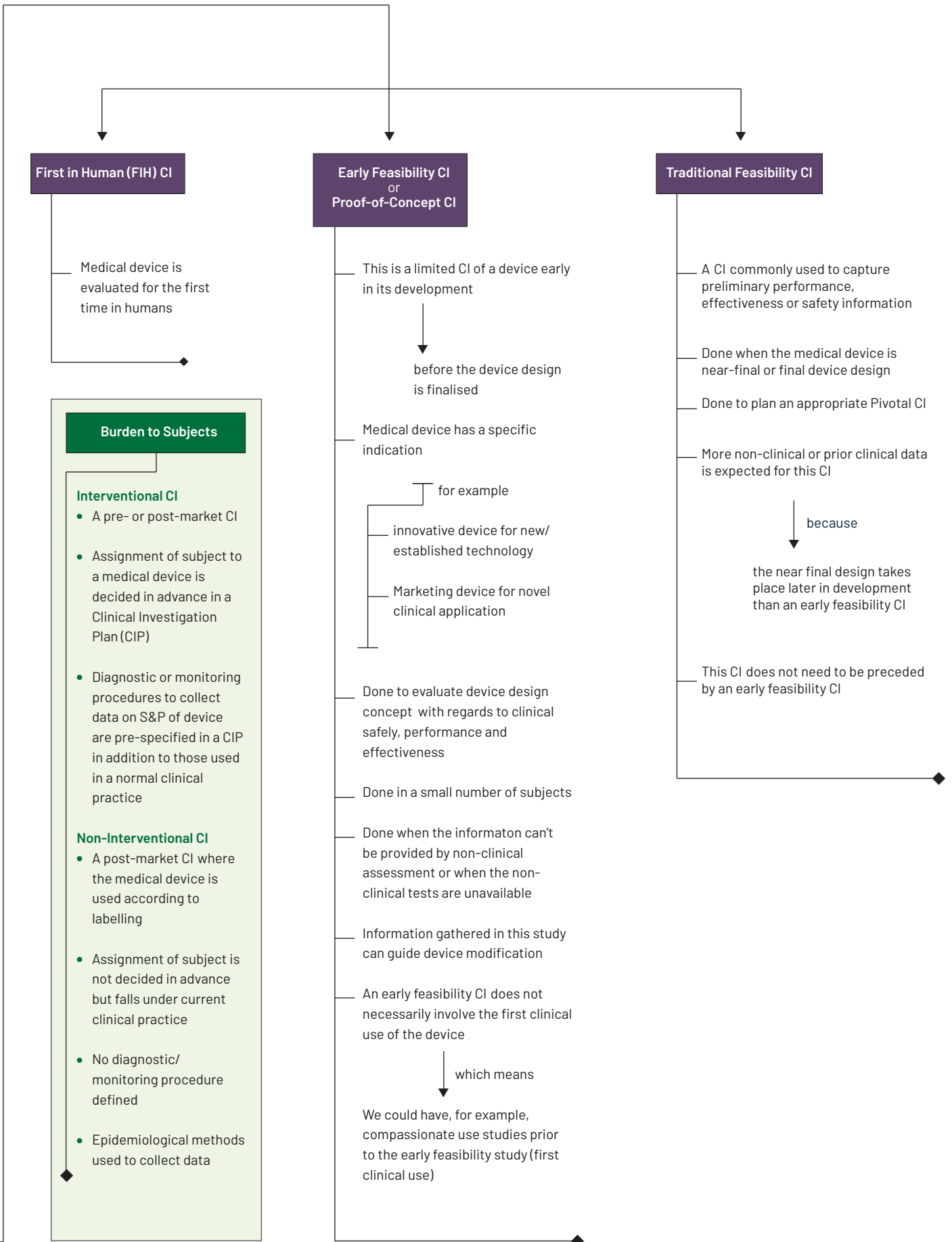
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Clinical investigation for medical devices – types and stages

Annex I of ISO 14155:2020 (International Organization for Standardization) helps define the various stages of clinical investigations for medical devices as well as the types of study designs. The following flowchart summarises Annex I, to assist those working in this domain, to better understand what each type of clinical investigation (CI) entails and facilitate with the medical device study designing process.







News and Notes from the World of Medical Writing

EMWA, AMWA, and ISMPP respond to baseless claims about medical writers

EMWA's Special Interest Group on Medical Communication initiated a reply to an article that made unfounded derogatory remarks about medical writers (MWs). Without providing any evidence, in an article about the development of randomised clinical trials in oncology (doi:10.1001/jamaoncol.2021.0379), the authors Del Paggio JC, Berry JS; Hopman WM et al. state:

There is reason to be concerned that medical writers may unduly influence the interpretation of trials. Additionally, their role is contrary to accepted scientific principles whereby first authors should take responsibility for writing their own manuscripts. This is an issue that requires serious discussion by clinicians and journal editors, as it is unlikely that medical writers have a neutral effect on the clinical trial reporting.

In the same section, they insinuate that the involvement of MWs in oncology RCTs is violating the authorship criteria of the International Committee of Medical Journal Editors.

The authors of the letter to the editor (Schindler T, Marchington J, Flores G; doi:10.1001/jamaoncol.2021.3341) point out that contrary to the accusations, studies have shown that the involvement of MWs in preparing manuscripts improves several outcomes, including better adherence to reporting guidelines, more complete reporting of trial results, a greater rate of publication over time, and a lower risk of publication retraction resulting from misconduct. Furthermore, the authors highlight that MWs are highly trained professionals, many with advanced degrees in life sciences, who help scientists achieve clear, objective, and understandable descriptions of study data. The letter adds that MWs are trained in good publication practice and that their

Thomas Schindler, Beatrix Doerr
EMWA Special Interest Group
on Medical Communications

organisations have developed principles of ethical conduct.

The letter to the editor was endorsed by leaders of three organisations – Beatrix Doerr for EMWA, Susan Krug for the American Medical Writers Association (AMWA), and Rob Matheis for the International Society for Medical Publication Professionals (ISMPP). This showcases the importance of ongoing alignment and exchange between the different MW organisations. MWs who come across published negative statements about medical communicators should inform the professional organisations to enable adequate responses. For the current case, everybody is welcome to submit further comments on the article page at the *JAMA Oncology* website.

Asian Council of Science Editors holds 7th annual conference

The Asian Council of Science Editors (ACSE) hosted its 7th Annual Conference, themed around “Pandemic Driven Scholarly Publishing: Ways to Ensure Future Resilience and Sustainability”, bringing together industry and academic experts to discuss the current status and future challenges to the Asian publishing industry.


The virtual conference was held August 21, 2021, and more than 200 people took part, including speakers, moderators, panel experts, and participants from a diverse group of countries including China, Korea, Japan, Thailand, the United States, the United Kingdom, Greece, Turkey, Egypt, Oman, Saudi Arabia, Nigeria, Pakistan, India, Iran, Australia, Malaysia, Argentina, and Indonesia.

The conference's platinum sponsors (Science Alert, Asian Network for Scientific Information

& Trend MD), gold sponsor (Science International, Asian Digital Library, ASCI Database), Silver Sponsors (SciONE, LiveDNA, and JournalsPedia), and collaborators (APII, AASSA, RCCIIT, NCT, ISMPP, AMWA, EMWA, ICP | UOK, J4R, FUI, and IINAMEI) made it a phenomenal success.

The conference commenced with the opening address of Dr Gazi Mahabubul Alam, chief advisor of the ACSE, followed by four sessions by distinguished speakers.

The first session was on various aspects of scholarly communication, publication, and editorial evaluation during the pandemic. The second session revolved around the topic of new technical tools to facilitate the publishing community. The third session featured five academic experts, who concluded with sharing their side of stories and opinions in facilitating

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pandemic-driven scholarly publishing. The last session looked at solutions, industry tools, and techniques to cope with the rising real-time challenges for the daily routine of editors and publishers. This was followed by a panel discussion on “Distraction, Modernism, and Creativity: Ways to Generate and Implement new Thoughts in Scholarly Publishing”.

For information about the ACSE annual conference, visit: <https://blog.theacse.com/2021/08/28/7th-acse-annual-conference-highlights/>. We would like to thank our esteemed speakers, panelists, and moderators for making this event a great success.

Regulatory Matters

SECTION EDITOR



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Biomarkers on my mind

Early in my regulatory medical writing career, I wrote several protocols in the cardiology therapeutic area. I was introduced to the cardiac biomarkers troponin I and N-terminal prohormone brain natriuretic peptide (NT-proBNP), which are indicators of cardiac injury and cardiac dysfunction, respectively. Before that, I had done a lot of work in oncology, and I was accustomed to biomarkers such as HER2 that can be used to define a patient population for a given treatment. It was at that point that I began to comprehend the diverse roles biomarkers play in drug development.

A biomarker is a *defined characteristic that is measured as an indicator of normal biological processes, pathological processes, or responses to an exposure or intervention*.¹ This definition is rather broad, and thus it is helpful to break this definition into more manageable pieces. The International Council for Harmonisation (ICH) E16 guidance on biomarkers describes their several purposes:²

- Selecting an eligible patient population for an indication or participation in a clinical study. These types of biomarkers can be used to identify individuals with a subtype of disease of interest. HER2 resides in this space: therapies such as trastuzumab are indicated for individuals who have HER2-positive breast cancer. This type of biomarker is of particular interest for precision medicine because it can predict response to therapy.
- Assessing disease state or prognosis. My good friends troponin I and NT-proBNP are in this category.
- Assessing the mechanism of action, including the mechanism of pharmacological mode of action, therapeutic effect, or toxicity.
- Optimising the dose.
- Monitoring drug response, both drug safety and drug efficacy.
- Maximising efficacy.
- Minimising toxicity.

As you can see, biomarkers can be used in a

variety of contexts: predicting an individual's risk of developing a disease, diagnosing a disease state, identifying a disease subtype, predicting a response to a therapy, detecting the effect of a therapy on an individual, monitoring the status of the disease, and monitoring safety.

Biomarkers come in many forms, including molecular, histologic, radiographic, or physiologic.¹ A lot of recent research has been devoted to genomic biomarkers, which can measure the expression, function, or regulation of a gene and serve as indicators of normal biologic processes, pathogenic processes and/or responses to therapeutics or other interventions.³ Genomic biomarkers include pharmacogenomic biomarkers, which are variations of DNA or RNA characteristics related to drug response. Because drug response includes the processes of drug absorption and disposition (pharmacokinetics) and drug effects (pharmacodynamics, drug efficacy, and drug adverse effects), pharmacogenomic biomarkers are becoming increasingly important for drug discovery, drug development, and clinical practice.³

Biomarkers can be used to predict clinical outcomes and accelerate the drug development process. Traditionally, clinical outcome assessments are used to support regulatory approval of therapies; however, a validated biomarker can also be used for regulatory approval for therapies. ICH E16 lays out general principles for qualifying biomarkers for submissions – that is, demonstrating that a biomarker reliably reflects a biological process, response, or event.² The submission for biomarker qualification is organised along the same lines as the Common Technical Document, with sections for regional administrative information, summaries, quality reports, nonclinical reports, and clinical reports.

Our hopes for personalised medicine rely on having sensitive (able to correctly detect true positives) and specific (able to correctly detect true negatives) biomarkers to tailor therapies to



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individuals. The biomarker space is continuously evolving, and I am gratified every time I encounter a new biomarker in my writing. The diverse potential of biomarkers is why I have biomarkers on my mind.

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Veterinary Medical Writing

SECTION EDITORS



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Editorial

This edition of Veterinary Medical Writing signals a changing of the guard as Karim Montasser passes on the reins, having guided this section of *Medical Writing* with a steady hand during his tenure. And it is mindful of those auspicious shoes to fill that we thank

Karim for his hard work and take up those reins. In this first issue, we thought we would ease you in gently; by introducing first ourselves and then our regular feature for the Veterinary Medical Writing section, From the horse's mouth. Here we offer MEW readers a window into what is making news in the veterinary world. Also,

Louisa Marcombes reflects on comparative medicine, which will likely be a hot topic at the EMWA Spring 2021 conference, and what it means from the veterinarian's perspective.

**Louisa Marcombes and
Jennifer Bell**

Meet the new veterinary section editors!

Hello! I am **Louisa Marcombes**, a freelance medical and veterinary writer based in Auvergne, France. After qualifying with a degree in Veterinary Medicine in 2001, I spent 20 years in small animal veterinary practice, mainly in London, UK. I worked in shelter medicine for ten years at Battersea Dogs & Cats Home, which gave me valuable experience communicating with the public. I even enjoyed a brief career as a TV vet! After Battersea, I was fortunate enough to spend 5 years teaching first opinion veterinary practice to final year vet students at the Royal Veterinary College. There I explored my interest in the effective communication of complex, evidence-based concepts. As well as my freelance work, I am currently a member of the clinical review



team of *inFOCUS*, an online veterinary journal watch published by the Royal College of Veterinary Surgeons.

And I am **Jennifer Bell**. I am a freelance medical writer based in Dundalk, Ireland, and I am not a vet. I have spent a lifetime loving animals and the natural history of our planet.

I have a life science education where I learned about animals, microorganisms, and various global environments. I have a PhD in Molecular Microbiology, BSc (Hons) in Animal Biology and an HND in Horse Studies. I concluded this education while living in the UK.



I returned to Ireland in 2010 and worked in human pharmaceutical and medical device industry quality departments between 2010 and 2018. During this time, I completed an MSc Pharmaceutical Manufacturing Technology course for professionals – an approved European pharmaceutical industry Qualified Person course. I have been a freelance medical writer since 2018.

As co-editors of the Veterinary Medical Writing Section of *Medical Writing*, we are delighted to have the opportunity to team up together and look forward to exploring the world of veterinary writing and helping to strengthen links between the veterinary and medical writing professions.

Comparative medicine: A view from the veterinary clinic

A *cat is not a small dog* is a phrase that all veterinarians are familiar with and is a mantra they will repeat to themselves throughout their clinical career. And for a good reason. It is a reminder that the anatomy, physiology, pharmacology, and pathology of the two species are not equivalent; that the clinical management of the cat for most conditions is unique from the dog's. Comparative medicine is central to veterinary science, and veterinarians in their daily practice

focus more on the differences between species than their similarities. So, how would the veterinarian in clinical practice view translational medicine – the use of clinical trial data from pets to advance both human and veterinary medicine – and its current renaissance as part of the One Health paradigm?

In his presentation at the opening session of the 2021 EMWA Spring conference, Dr Craig Woods, DVM, of the Institute of Healthcare

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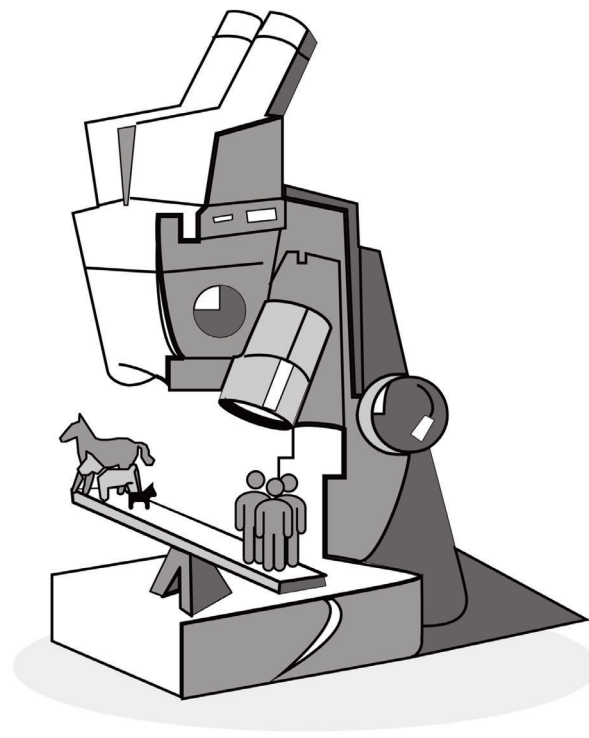
Innovation at Midwestern University, Arizona, US, discussed the increasing importance of translational medicine in pharmaceutical research and development. With only 10% of compounds

entering phase 1 trial eventually reaching the market¹ and the estimated average cost (\$1.3 billion/1.07 billion euros)² to develop a human pharmaceutical therapy, the consensus is that the current drug development model is unsustainable. Dr Woods explained that existing research and development, which uses data from laboratory animals to select therapies for human clinical trials, was a major reason for the high attrition rate of phase 1 compounds. In other words, a mouse is not a small human. Researchers are now exploring the potential of owned pets, with their spontaneous disease and quasi-human lifestyles, to bridge the gulf between the laboratory and the real world. Dr Woods gave the example of work carried out by Ohio State University Veterinary School in partnership with the Nationwide Children's Hospital in the US.³ This collaboration has been the driver behind the research effort to identify the biologic pathways that govern metastasis in osteosarcoma. The goal is to develop a screening modality that not only identifies canine patients with osteosarcoma at elevated risk of metastases but also use this new technology in paediatric patients.³

The translational medicine paradigm signals a move away from the traditional professional silos that have been a barrier to academic and clinical collaboration between vets and doctors.⁴ As a medical writer with a veterinary clinical background, these are my reflections on what comparative medicine looks like from the veterinary clinic. Given the “cat is not a small dog” dogma, how easy will it be to persuade the veterinary professional that the cat is a small human, albeit in very specific and clearly defined circumstances?

Comparative medicine: A shot in the arm for veterinary clinical research

The premise of translational medicine is that it harnesses the research potential of companion animals. However, it is fair to state that much of the narrative focuses on the potential gains for human healthcare. Non-human healthcare is often an afterthought, if it is mentioned at all. Veterinarians, for obvious reasons, have much invested



in the advancement of human medicine. However, they also spend their entire professional lives focused on animal health and welfare, and this will always be their first consideration in dialogue about comparative medicine. Therefore, when writing about translational medicine, remember to emphasise the potential gains to non-human patients as well as the human ones, particularly when addressing a veterinary audience.

Vets want more drugs for their patients. The high cost of drug development and the smaller pharmaceutical market means that veterinarians have access to relatively few licensed medications in their practice. Comparative medicine can accelerate veterinary drug development and has already been credited with bringing several novel therapies closer to clinical usage. The Bruton Kinase inhibitor ibrutinib (Imbruvica, Janssen-Cilag Ltd), used to treat B-cell malignancies in humans (based on data from a spontaneous lymphoma canine model), has been investigated as a possible treatment for canine mast cell tumours after it was observed to block IgE activation in human mast cells.⁵ Cognitive dysfunction in geriatric cats has attracted interest as a model for Alzheimer's in people, and cannabidiol has been flagged as a possible treatment for cognitive decline in both species.⁶ Mavacamten, a first-in-class allosteric

modulator of cardiac myosin, should soon be the first authorised targeted therapy of hypertrophic cardiomyopathy (HCM) in humans.⁷ Data on the efficacy and safety of cats with HCM were central to the development of mavacamten.⁸ As a result of this translational research, physicians and perhaps veterinarians will have an effective, targeted treatment for this common disease.

Conflicts and challenges: Where aims and objectives diverge

There are significant obstacles to bridging the gap between veterinary and human clinical research, which are yet to be fully addressed by the scientific community. During her talk at the EMWA 2021 spring symposium, Dr Rachel Dean, Director of Clinical Research and Excellence in Practice at Vet Partners, UK, discussed how the quality of veterinary clinical trials compares negatively with human clinical trial standards. Dr Dean characterised veterinary clinical trials as often asking the wrong research question and being hampered by poor study design. For example, a 2016 study showed that 87% of the papers assessing treatment efficacy in medical journals are based on a randomised controlled design.⁹ This proportion drops to only 52% of comparable trials in veterinary journals. Although in the long-term translational medicine offers veterinary clinical research an opportunity to level up, these discrepancies in clinical trial quality can't fail to be a limitation at present.

And how about the pet version of the declaration of Helsinki? Experiments on animals in the laboratory setting are regulated in the EU under the Directive 2010/63/EU and built on the 3Rs principles of reduction, replacement, and refinement. But what about client-owned pets? In the UK, the veterinarian must determine whether a proposed treatment is a legitimate act of veterinary surgery (as a “recognised veterinary practice”) or whether it is a scientific study, in which case it falls under the auspices of The Animals (Scientific Procedures) Act 1986¹⁰ with accompanying licensure. The difficulty is that there is a sizeable grey area in clinical practice where this judgement can be hard to make, and avoidable harms have occurred as a result.¹¹ Despite this, there are calls to relax the existing regulation to make the use of pets in clinical trials easier to carry out.¹²

Finally, there is the pet's owner to consider.

A recent study compared the priorities of the main stakeholders in research in canine epilepsy research¹³ and found that the priorities of clinicians and owners were not aligned. Clinicians were found to place more importance on clinical outcomes and long-term implications for managing or preventing idiopathic epilepsy. In contrast, pet owners were more concerned about immediate impacts on their pet's quality of life, adverse effects, and comorbidities. This highlights the risk of mismatched expectations between clinicians and owners. Prioritising owner-reported outcomes in comparative medicine takes on extra importance when we are reminded that euthanasia is a treatment option in veterinary medicine. Translational research should, above all other considerations, never make this outcome more likely.

What's in a word? Comparative or translational?

Dear reader, you may have noticed that the terms “comparative” and “translational” have been used interchangeably in this article. This is partly deliberate, but I also have tried to mirror their use in the literature. The semantics, arguably, are important. Here is the definition of translational medicine provided by the European Society of Translational Medicine:

“...an interdisciplinary branch of the biomedical field supported by three main pillars: bench side, bedside and community”.¹⁴

Note there is no mention here of animal health in this definition. Furthermore, the word “veterinary” does not appear once in this citation. A definition of comparative medicine is equally

esoteric: “‘Comparative Medicine’ may be defined as a field of study concentrating on similarities and differences between human and veterinary medicine.”¹⁵ At least here animal health is explicitly referenced. The term “reverse translation” has been proposed elsewhere^{6,16} to signify a benefit for veterinary species. Indeed, the definitions of and distinction between “translational medicine” and “comparative medicine” are woolly and need refining.

It is reasonable to state that, at present, comparative medicine does not have the visibility it warrants within the veterinary profession, and most vets in practice would struggle to define it.

Perhaps that is not surprising as a universally accepted definition appears not to exist. Indeed, there is, in my view, a need for terminology that clearly distinguishes research that is based on laboratory animals who happen to be a companion animal species from that derived from client-owned companion animals. The cats used in the HCM study mentioned above, for example, were unowned, purpose-bred colony cats that underwent an experimental procedure and not a clinical trial. Few veterinarians

would recognise them as real-world veterinary patients. The use of current terminology in the literature makes it very hard to make this vital distinction.

Comparative medicine has the potential to advance human and animal healthcare in the One Health framework. However, there needs to be a shift from the status quo through closer integration of medical and veterinary professions. From improving the geographic and intellectual proximity of the respective faculties

This can only be brought about with terminology that is unambiguous and accessible not just to biomedical professionals but also to society.

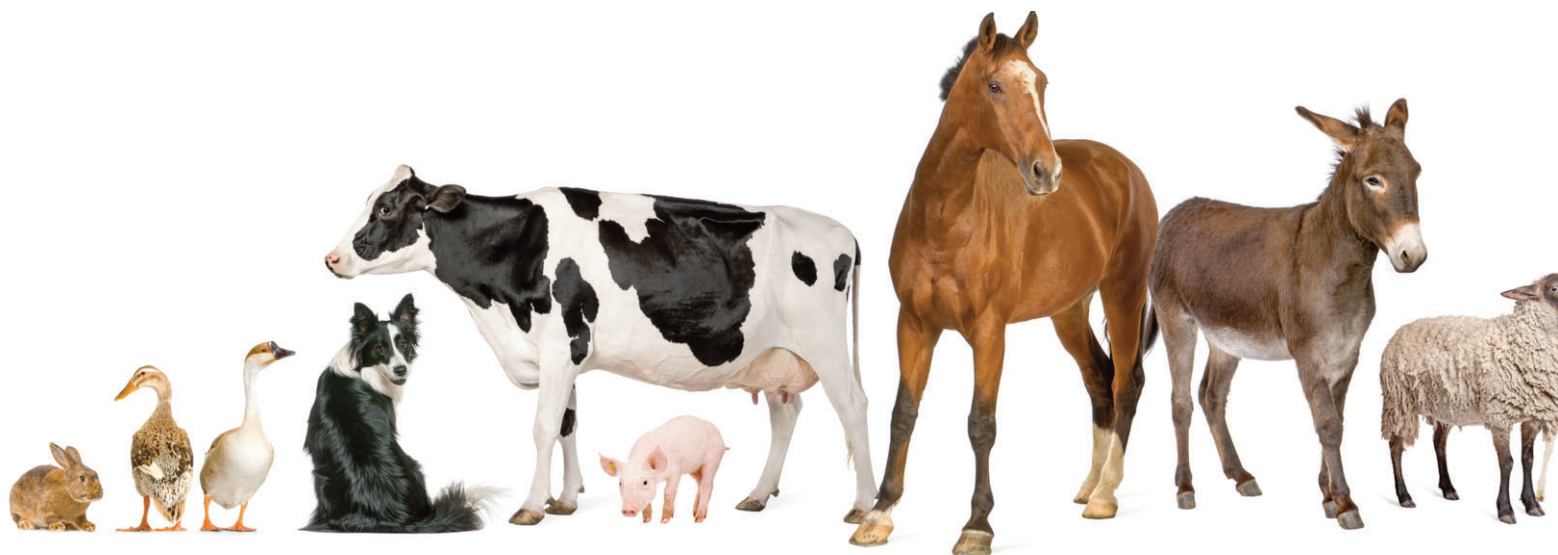
at academic institutions to elevating literature databases from their silos by creating a One Literature.⁴ This can only be brought about with terminology that is unambiguous and accessible not just to biomedical professionals but also to society. Medical communications professionals are exceptionally well placed to lead with this.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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From the horse's mouth



The quarterly pick of the news from the veterinary world

An increased incidence of pancytopenia (low counts of red and white blood cells and platelets) in cats in the UK has resulted in a pet food manufacturer recalling its products, it was reported by the *Veterinary Times* in June 2021. Since May 2021, veterinarians across the UK have reported an increase in pet cats presenting with pancytopenia. The Royal Veterinary College, London, had recorded at least 539 cases by August 9, with a mortality of 63%. Epidemiological analysis of confirmed cases has pointed to a possible dietary factor that has prompted the Food Standards Authority in the UK to issue a product recall of hypoallergenic cat food manufactured by Fold Hill Foods, including products from their “Applaws” and “AVA” ranges. Studies on this “Feline Pancytopenia Syndrome” by the Royal Veterinary College are ongoing to identify the underlying cause of this phenomenon. Meanwhile, veterinarians up and down the UK have experienced an increased volume of calls from worried owners since the Food Standards Authority announcement was made.

Goa has become the first Indian state to declare state-wide control of rabies, hailed as a breakthrough in the global fight against the disease, the UK-based charity Mission Rabies has reported on June 23, 2021. Mission Rabies has been working with the state since 2013, when one rabid dog was being collected every 3 days. The success of this rabies control programme has been attributed to an aggressive canine vaccination programme, where at one point, 61,143 dogs were vaccinated in 30 days, the provision of rabies education to 1 million people, and the implementation of a rapid-response surveillance team. As a result, there have been no human deaths from rabies reported in the state since 2018. With statewide rabies control declared, the Goan government has the authority to enforce dog vaccination, and unvaccinated dogs are now prevented from entering the state.

Boehringer Ingelheim has announced a partnership with Lifebit Biotech Ltd, a London-based company specialising in the development of genomics and bioinformatics platforms, as reported in the *Veterinary Times* on June 9, 2021. The Lifebit REAL platform uses AI technology to analyse real-world data obtained from scientific publications and other open-source sites to detect animal disease outbreaks. By assimilating vast amounts of data in a time scale that has, until now, not been possible, it is hoped that this technology will not only enable faster detection of disease events but also be a valuable tool for targeting R&D efforts.



Medical Communications and Writing for Patients

Editorial

Dear All,

In this edition of *Medical Writing*, I'm delighted to present an article from Vidhi Vashisht and colleagues on a subject very close to my heart – plain language summaries (PLSs). PLSs are summaries of clinical trial results written in a format that is understandable to the general public. They are required by the latest regulatory requirements, but writing for this audience is very challenging and requires

different writing skills and approaches to “translate” complex scientific information into a form that is not only understandable but meaningful for a “lay” audience.

The current guidelines recommend the inclusion of the target audience in the review of PLSs, but patient involvement at any stage is not currently mandated by the regulations. In this article, Vidhi Vashisht et al., beautifully explain their experience of involving patient panels in the production of PLSs, and describe the added

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benefits and insights they have gained by doing this.

I hope that you enjoy Vidhi's article as much as I did.

Bestest,
Lisa

The value of patient voices in plain language summaries



Introduction

Plain language summaries (PLS), also known as lay language summaries, are summaries of clinical trial results written in a format that is understandable by “laypersons”.

They are required by the European Medicines Agency (EMA) through the EU clinical trials regulation 536/2014 (Article 37) in an effort to increase clinical trial results disclosure and transparency.¹

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The goal of a PLS is to make clinical trial results available to clinical trial participants, patients, and the general public in language that is easy to understand without compromising scientific integrity and accuracy. It is also required that the content be unbiased and non-promotional. As laid out in the recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use,² PLSs should be written at a proficiency level of 2 to 3, which roughly corresponds to a 6th to 8th grade reading level. Furthermore, careful consideration of the flow of information, document layout, and use of visuals to present clinical trial results can greatly increase the comprehension of complex information for

readers who are not familiar with the intricacies of clinical trials.

The EU-CTR guidelines¹ also encourage the involvement of patients, patient representatives, advocates, and members of the public in the development and review of the summary to assess comprehension and the value of the information provided.

Patient panel review of PLSs

Background

As PLSs are written for the general public and patients, it is strongly recommended that a patient panel review be conducted to ensure that the summary is clear and understood by the target audience. This review is sometimes also referred to as user testing, readability testing, or patient advocacy review, and is recommended by the EU CTR guidelines.

This article describes our experience of feedback from patient panel reviews of our PLSs.

To conduct the PLS patient panel review, panelists are recruited in the country for which the master PLS is written. For instance, when writing US English PLSs, panelists are from the United States.

- The criteria for being on a PLS panel is to be: familiar with the medical condition for which the PLS is written, which can be as either a patient, caregiver, immediate family member,

or close friend.

- enthusiastic about research, although a panelist does not need to know about current research or be able to understand complex scientific terminology.
- able to listen to others and express his or her own views during the discussion.

Methods

Potential patient panel reviewers are identified through online forums, patient advocacy groups, and other networks based on the medical condition described in the PLS. Once the panelists agree to be a part of the panel, a written confidentiality agreement and guidance document are provided with instructions on how to join the discussion. The panelists are informed that the purpose of the panel discussion is to gain feedback on the clarity and readability of the PLS and the intention is not to promote any drug.

Panel reviews are conducted in an interview-style format, using a structured, two-way discussion to get solicited and unsolicited feedback on the PLS. Panelists are asked to

From this

A clinical trial to find out if study drug can improve the eyesight of participants with **presbyopia**.

To this

A clinical trial to find out if study drug can improve **presbyopia**, the inability to see objects up close

About this summary

This summary is written to share the results of this clinical trial with the public in simple language. It describes why the study was needed, how it was done, and the results.

Figure 1. First impressions matter

provide their opinion on aspects of the PLS that are of specific interest to the clinical review team. Panelists are also encouraged to provide general feedback on all sections of the PLS, especially if any part is not easy to understand. Panelists are also asked to explain the results in their own words to confirm that the intended message is

Total Mayo Score (TMS)

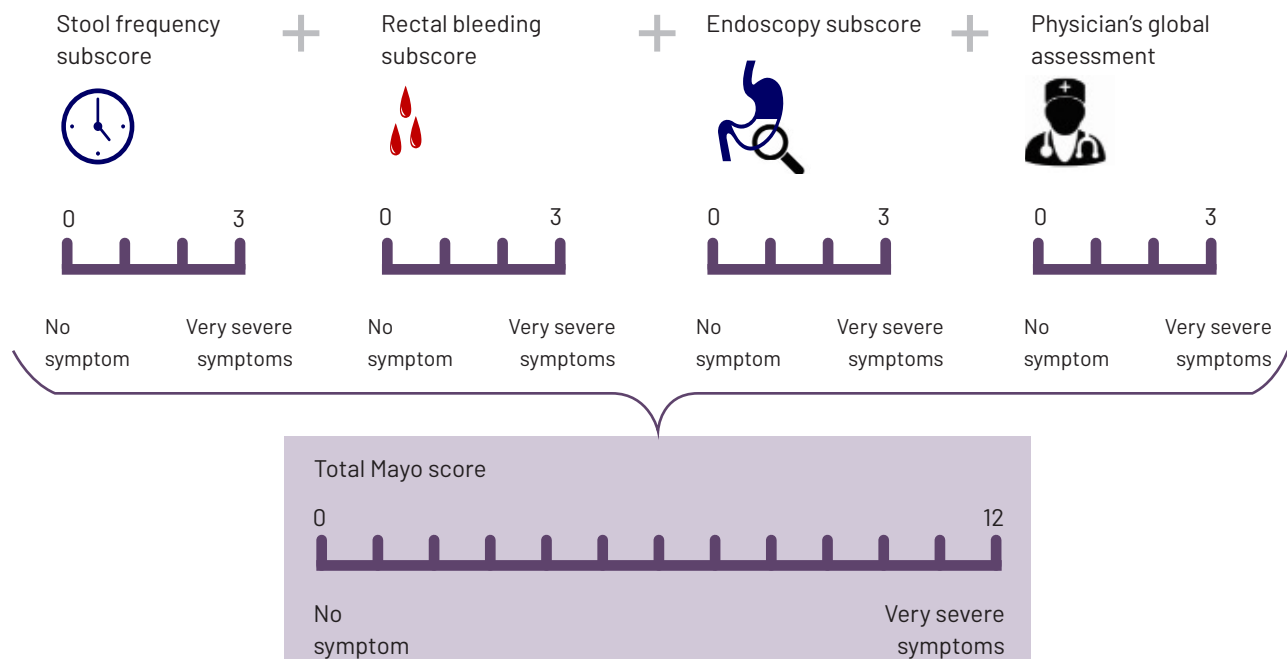


Figure 2. Visuals to explain scales

clearly reflected in the PLS. After the panel, a collated feedback report is created by the PLS writer for the clinical review team. This includes recommendations on how panel feedback could be addressed. After the recommendations are discussed and agreed upon with the clinical review team, updates are made to the PLS.

Learnings from patient panel discussions

The patient panel feedback on the PLSs written by our team over the past 3 years has helped us to identify the following improvement areas for PLS readability and comprehension.

First impressions matter

The first page sets the tone to help readers understand what the PLS is about and what information they will get by reading it.

- Create a study title that is clear and informative, providing a simple description of the condition for which the PLS is written (Figure 1).
- Add an introduction that explains what the document contains and why it has been written (Figure 1).
- Add context: inform the reader that the PLS

Panelists are also encouraged to provide general feedback on all sections of the PLS, especially if any part is not easy to understand.

only shows the results of one clinical trial and that broad interpretations about efficacy and safety, as well as health decisions, should not be based on the contents of this one document.

Be aware of jargon

The EU-CTR guidance suggests that the PLS should be written in everyday language. This should be reflected throughout the document. Without testing the PLS with the intended audience, a

writer can only assume that the PLS is understandable. Conducting patient panel reviews allows writers to identify what technical or specialised terms, or jargon, should be simplified.

- Panelists recommend that scientific terms be simplified, or defined, in a way that can be understood by a non-scientific audience. For example, replacing “safety assessments” with “health check-up”.
- When discussing technical scientific concepts, such as mechanism of action, it is helpful to define technical terms that may not be well known outside of the industry. For example, if the study drug impacts expression of a protein linked with the disease, or if a

certain enzyme or protein is being measured by researchers because its levels reflect whether or not the study drug is effective, panelists recommend adding additional text to connect the dots for the reader on why certain measures are important and what they imply. Readers find this informative and helpful, rather than having the PLS simplified to the extent that the rationale behind the study and study assessments is unclear.

- To provide another example, biomarker assessments are also of interest to patients. However, because of the technical nature of such results, it is recommended that the meaning behind each assessment is clearly laid out in simple terms, so that readers can draw conclusions from the data themselves, instead of having it “told” to them.

Data and patient reported outcome scales are understood better as visuals

Visuals, whether in the form of diagrams, graphs, or infographics, have been shown to greatly support the understanding of complex data. Discussions during patient panels confirm that visuals are preferred over an “all text” format.

- Scales used to describe severity of symptoms, as well as categories of information, are better presented as images rather than text in a document for the public (Figure 2).
- Panelists also recommend reiterating if

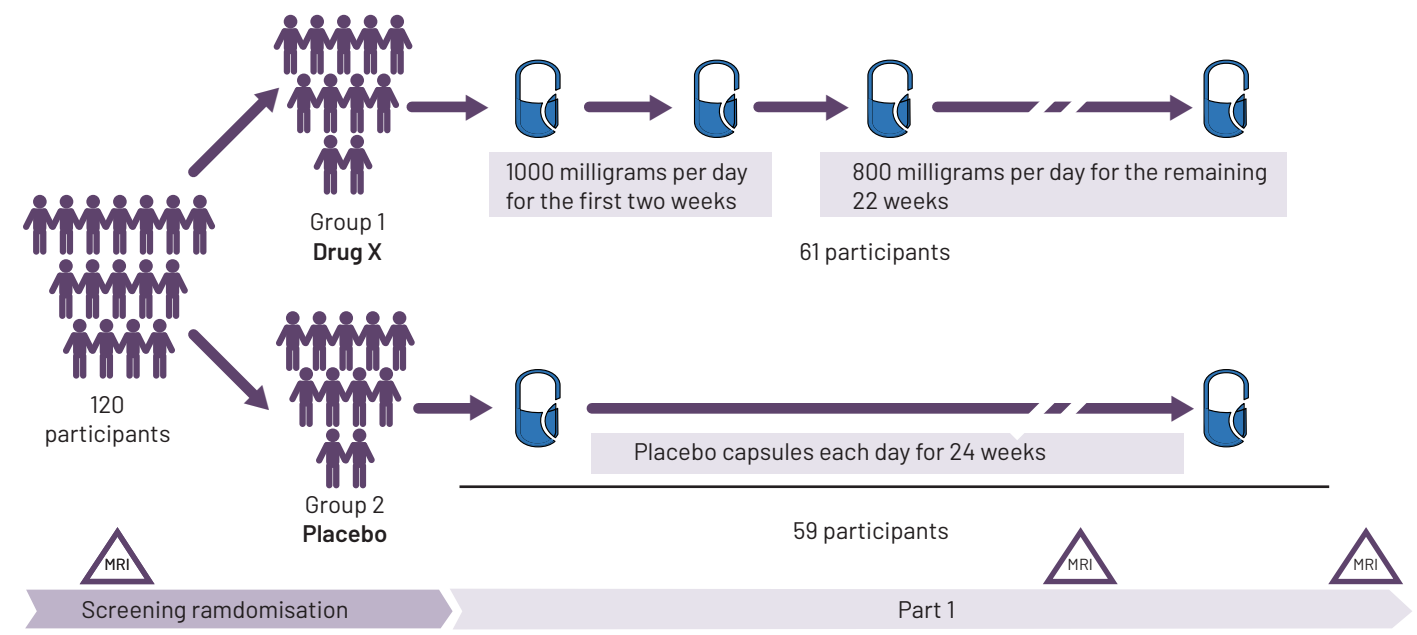


Figure 3. A simple visual for the study design

higher or lower values on a graph correlate with positive or negative outcomes for the patients. Although this information could be pieced together based on the introduction and study design sections, making results and figures standalone components that can be easily interpreted by readers has been found to be crucial in improving readability.

- Panelists feel that consistently using the same colors for specific treatment groups throughout the PLS allows them to more easily connect the information presented in the study design with the efficacy and safety results.

It is important to note that there should be a careful balance between the use of relevant infographics that aid the understanding of important concepts and text in the PLS. If not chosen carefully, or if relied on too heavily, visuals can also lead to confusion for the reader as they are subject to interpretation.

Leverage the study design to increase transparency

Explaining the study design helps to provide context for the clinical trial results. The study design description and figure should be specific, allowing readers to easily understand what type of assessments were done, how the study drug was given, if there was an impact on other

medication that was being taken, and what type of a time commitment was required. Discussion during patient panels suggests that readers are interested in details such as route of administration, impact on concomitant medication, and timelines of the various periods of a clinical trial.

All of these factors can be incorporated into the study description and design of the PLS, an example of which is provided in Figure 3.

Don't forget your audience

While writing PLSs, the considerations for the target audience should not be limited to layout and word choice. Keep in mind any customisation of the PLS that can be done to make the information easily accessible to the patient population based on the medical condition or therapeutic area for which it is being written.

- For studies related to eyesight loss, larger font should be used to make the PLS easier to read. If possible, an example image can be added to demonstrate what type of eyesight loss is experienced by someone with that condition (Figure 4).
- In studies with paediatric patients, additional infographics and images should be incorpo-

If not chosen carefully, or if relied on too heavily, visuals can also lead to confusion for the reader as they are subject to interpretation.

rated to explain the content of a PLS. More white space should be intentionally kept in the document, as children can be easily overwhelmed by paragraphs of text.

- Cultural, geographical, and individual experiences may impact how readers interpret or understand the information in a PLS. Additionally, rescue medication or standard-of-care drugs may be marketed by different names in different countries. For example, an inhaler used as rescue medicine is known in different countries as “salbutamol” or “albuterol”, so both were included in a recently written PLS based on feedback from the patient panel.

Be respectful

Finally, panelists regularly highlight appreciation for language that is respectful of the patients. Therefore, it is strongly recommended that writers be mindful of the terminology used in the PLS, differentiating it from other documents that focus on the experimental nature of clinical trials.

- Use empowering language so that the study participants feel respected.
 - ✓ Use the term “**participants**” instead of “**patients**” or “**subjects**”.
 - ✓ Use the term “**condition**” instead of “**disease**”.
 - ✓ Use “**treatment did not benefit the participants**” instead of “**participants failed the treatment**”.
- Be extra sensitive while writing PLSs about conditions that have associated social stigma, such as mental illness.
- A small component that is often appreciated by panelists while reading PLSs is the thank you note acknowledging the time and effort of participants without whom clinical trials would not be possible (Figure 5). This is also recommended by the EU-CTR guidelines.¹

Conclusions

The feedback we have received from our patient panels agrees with recommendations by the EU-CTR guidelines and with health literacy principles. Nowadays, more than ever, there is a demand for transparency and engagement of patients in clinical trials. PLSs provide an avenue through which clinical trial results can be shared with the general public in a way that is both meaningful and easy to understand. However, since PLS writing is different from traditional medical and regulatory writing and has a different target audience, it is important to take into

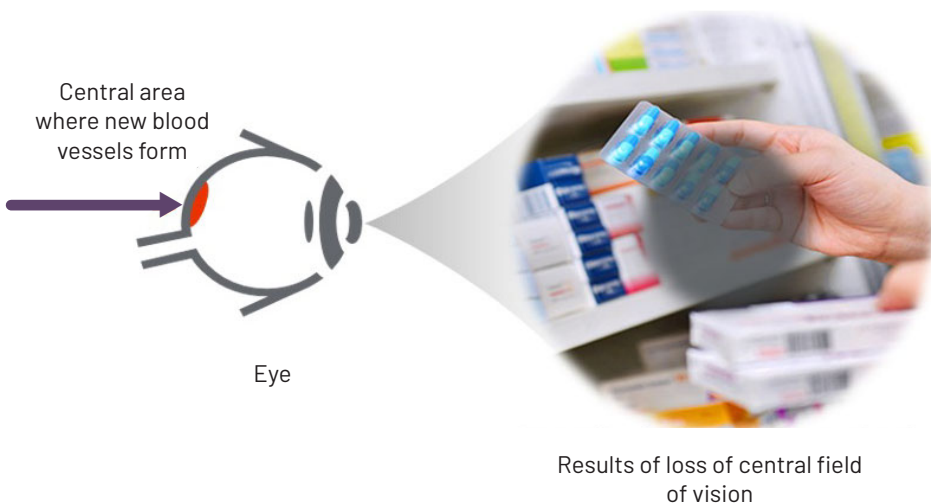


Figure 4. Special considerations for the readers



Thank you to the study participants!



Thank you for taking part in this clinical study for Condition X. Your time and commitment has helped us move one step closer to bringing better treatments to patients.

Figure 5. Showing appreciation

account the perspectives and opinions of the public and patient population for whom these documents are being written. The best way to test the effectiveness of this document is by conducting patient panel reviews and soliciting feedback from people familiar with the medical condition for which the PLS is written.

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Disclaimers

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

Conflicts of interest

The authors declare no conflicts of interest.

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My First Medical Writing

SECTION EDITOR



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Editorial

In this release of My First Medical Writing, I have the pleasure to share great articles written by two aspiring medical writers. Nesrine Benhizia-Benaouicha, MD, is a clinical trial manager and academic medical writer at the emergency department in Nantes University

Hospital, France, with extensive experience in clinical trial management and recruitment in the ER. Sofia Polcownuk has a PhD in biology from the University of Buenos Aires, Argentina, and is currently a research associate at the University of Glasgow, UK, focused on understanding the gut-brain axis. It has been a pleasure working

with both Nesrine and Sofia in publishing their first articles in *Medical Writing*. If you're an aspiring medical writer eager to gain experience in this field, this space offers you an opportunity to publish your work and start creating your portfolio.

Evguenia

Clinical trial management and patient recruitment in the emergency department

Everyone is probably familiar with *ER*, an American television series created by Michael Crichton that aired on NBC for 15 years. In that fictional emergency room, many popular topics were discussed between patients and physicians, for example, HIV status, the catastrophic situation in Congo-Kinshasa and Darfour, deafness and sign language, euthanasia, and Social Security problems.¹ However, did you know that in a real ER, or emergency department (ED) as it is more formally known, the physicians are also conducting and discussing clinical research projects?

Emergency medicine is a universal and transversal discipline at the junction of several disciplines. It is a science of acute pathologies and the overall management of the patient. The major asset of emergency medicine lies in the diversity of its practices, which includes triage, pre-hospital emergency care, emergency response for disaster management, etc. Otherwise, within the ED, physicians don't just manage critical situations, they also conduct research, as in any other other speciality. This is made possible due to the recognition of emergency medicine as a stand-alone speciality, which is the case in the US and in 17 countries in the European Union with national and international scientific conferences.²

The strength of a discipline's research is also measured by its organisation and the dissemination of knowledge. In a recent Canadian survey assessing the level of development of the emergency medicine system in 36 countries, 70% of the nations had national emergency medicine

research.³ Emergency medicine is widely represented in the international scientific literature. There are six international Anglo-Saxon and two European indexed journals dedicated to emergency medicine, including the *American Journal of Emergency Medicine* and the *European Journal of Emergency Medicine*. The major generalist scientific journals (e.g., the *New England Journal of Medicine*, the *Lancet*, and the *British Medical Journal*) also devote considerable space to clinical research in emergency medicine. Clearly, research is a priority for emergency medicine as it is for non-



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emergency medicine.

Research provides the foundation for everything we do in medicine. In particular, bedside clinical research, in which patients are prospectively enrolled in clinical trials, including those that compare therapeutic strategies, is important to efficient and cost-effective patient care.⁴ However, bedside research in the emergency



Photo: Alamy

context presents a number of challenges. Indeed, the emergency and pre-hospital environments are unlike any other clinical environment and require special consideration to allow the successful implementation of clinical trials.⁵ In addition, research projects in emergency medicine are not limited to this speciality but often involve the collaboration of multiple specialities such as cardiology, neurology, infectious disease, etc., due to its transversal nature and that the ED is the gateway for the patient who enters the hospital. Rightly so, emergency departments across the world are becoming increasingly crowded. The numbers and the complexity of patients arriving in the ED are increasing.⁶ The caregivers have neither the time nor the resources to help with research, making it a challenging environment to incorporate clinical research in addition to providing effective and timely care.

With this in mind and considering the complexities of implementing a protocol in an emergency context, when designing project research, investigators need to make sure the intervention and flowchart of the trial are not overly complex and should demonstrate that participants are available for recruitment into their studies. Hence, emergency medicine researchers should optimise the design and implementation of trials to accommodate the ED setting that must include only key intervention and data points while adhering to the regulatory framework of clinical research. In order to do that, they should work with clinical research staff early in the protocol development. That staff can include clinical project managers, study coordinators, biostatisticians, pharmacists, and medical writers. They would help to guide investigators during the trial design in an effort to maximise study efficiency in the ED environment. Therefore, involving clinical research staff is an important way to improve successful implementation, in order to take advantage of the millions of ED patients who could be eligible to participate in clinical trials. It is also essential to provide evidence that a sufficient number of eligible subjects can be enrolled in the protocol in a timely manner, which is crucial to receiving funding.

When implementing trials in the ED, one must focus on identifying participants who meet eligibility criteria to enter prospective studies. In each trial, inclusion and exclusion criteria must

be defined, for example, you must be female (inclusion criteria) and not be pregnant (exclusion criteria). The screening and identification of participants are other significant challenges in the ED, where timing from arrival to the need for treatment is tight (e.g., a research project about acute pain management, acute health failure, etc.). Physicians identify potential obstacles to

recruitment, such as real-time identification of eligible participants and consent issues. That said, there are specific strategies to enhance recruitment into trials.

For example, when using Electronic Medical Records (EMR), software can provide a timely and efficient method of identifying participants. This software connects to EMR for screening of existing medical data and when a study matches

the patient's medical record, an alert is sent in real-time through central paging to the physician and study coordinator. For example, we want to select patients who have a prescription for a particular antibiotic. When the physician prescribes this antibiotic in the EMR, an alert is sent with this message: "This patient is potentially eligible for project X, please contact research member staff". Such software has been used successfully to recruit participants into prospective studies. There has been an increase in the number of enrolments in a study using clinical trial alerts within an EMR.⁷

But this software is not the only tool used to alert research staff of potential participants. Other alerts include study documentation sheets included in kits (e.g., in lumbar puncture kits for meningitis studies), advertising posters, and leaflets with concise information about ongoing recruitment for studies.

Another way to further research is when research staff, physically present in the ED, work closely with clinical teams and can be involved from identification and recruitment of the patient to the final follow-up visit in the trial. They can manually review electronic medical records of admitted patients to screen potential participants. A study coordinator or a specific research staff member (e.g., a study nurse), who is either dedicated to reviewing current patients in the ED or the alert in central paging, is essential to capture all eligible participants.⁸ Many academic EDs have invested in research personnel. The skills and experience of these individuals to enrol patients into interventional clinical trials are proven. The funding is often being shared across

multiple projects. Therefore, there needs to be enough volume of patients and studies to justify the effort and cost of their full-time presence.⁹

Moreover, research staff support physicians to obtain informed consent from the patient to take part in a clinical trial, which must be written, dated, and signed. According to Good Clinical Practices, a clinical trial may be undertaken only if the trial subject had the opportunity, in a prior interview with the investigator, to understand the objectives, risks, and inconveniences of the trial and they are able to give informed consent, or a legal representative may do so when the patient is not able to give informed consent. But, obtaining consent in the ED is nearly always problematic. The time frame available to recruit participants in emergency medical clinical trials is often far tighter than for standard trials.¹⁰ Patients are frequently sedated, unconscious (e.g., cardiac arrest), or, when conscious, are stressed and highly dependent on the medical team. Likewise, the legal representative is rarely on the spot.¹¹

Exception From Informed Consent (EFIC) has been used successfully to enrol participants into research in the pre-hospital and ED setting when a patient or their legal representative are not available. EFIC allows the enrolment of participants into studies without prior consent when the following criteria are met:

- it must be a life-threatening situation,
- available treatments are unproven or unsatisfactory,
- participation in the research holds out the prospect of direct benefit to the participants,
- and the clinical investigation could not practicably be carried out without the exception and the Office of Human Research Protections, which must allow using this EFIC.¹²

However, even if consent is waived before enrolment, the notification must be done and consent obtained from the patient or legally authorised representative as soon as possible.

Finally, research staff members are also involved in the follow-up of the patients. Indeed, a key for a successful study is time to follow-up with participants. The follow-up in emergency medicine clinical trials must be short (e.g., hospital discharge or on day 28) and by phone. Clearly, the longer the follow-up, the greater the risk of losing patients. There is also the risk of protocol violations and refusing patient refusal to schedule a follow-up visit. These risks can be minimised with strict oversight by research staff members. Indeed, they should be in close contact with participants and record telephone follow-

ups in a log, keeping track of the best times to contact the patient. While it is generally ideal to have a phone follow-up, this can also be done through research units with their research staff (e.g., study nurses) scheduling follow-up visits according to the availability of physicians. Furthermore, if participants should be given study-specific visits, consider who have physical and logistical difficulties returning for follow-up.

Otherwise, if participants are compensated for transport costs to themselves and their visits are at no cost, they are more likely to remain in the study.

Clinical research in emergency medicine is an evolving field. Currently, new projects are being developed in the field of big data, artificial intelligence, and machine learning. Artificial intelligence can improve emergency care, help with diagnosis and manage patient flows. Research in emergency medicine has a bright future ahead.

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A gut-feeling: How intestinal diseases can affect our sleep

Do you lie awake at night feeling that something bad may happen? You might think that you are crazy, but don't worry, you are not alone. Almost every animal carries in their gut microorganisms such as bacteria, forming the microbiota, a complex community of different species living in their intestines. These microorganisms influence our health and fitness. There is a deep connection between what is happening with the microbiota in our gut and changes in our sleep patterns. The bacteria in our intestines can influence sleep by communicating with the brain through the gut-brain axis.

Gut-brain axis

The gut and the brain have a close relationship and communicate with each other in two different ways:

- The nerves around the intestine, the enteric system, receive and send signals to and from the brain.
- The microbiota themselves send messages to the brain.

The microbiota releases small molecules, called neuropeptides, and hormones. In the intestine, these molecules are absorbed and finally reach the blood. Through the circulatory system, these signals contact the brain where they bind to receptors, unleashing different physiological or behavioural changes.

Sleep problems and gut disease

Researchers have found a strong relationship between insomnia and gut disorders. Patients who suffer from intestinal problems often report more frequent night-time awakenings, while other patients who suffer from more aggressive gut diseases, like colorectal cancer, also report that the duration and quality of sleep are affected.¹ The bacterial composition of the gut in patients with cancer is different compared to healthy people and this difference in the microbiota is strongly associated with the quality of sleep.¹



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Red flag for colorectal cancer

Experiencing some discomfort in our intestine once in a while is normal, but when it occurs often, we need to be alert. Intestinal inflammation and changes in our bowel habits or sleep patterns have been researched as red flags for the beginning of colorectal cancer. These changes may potentially allow an earlier diagnosis, improving treatment and survival.²

Colorectal cancer and microbiota disruptions

Our gut bacteria help us maintain intestinal homeostasis by regulating biological functions (like immunity), protecting our intestine, and regulating our metabolism. Colorectal cancer is

Amongst the small molecules that the bacteria produce, short-chain fatty acids are very important.

These molecules are produced when the bacteria ferment the fibre we eat and have a positive effect on the gut, in particular on the intestinal mucosa. In the gut of patients with intestinal problems, like inflammation, there is a reduction of these molecules compared with healthy individuals.



one of the most common cancers worldwide and one of the most aggressive gut diseases. Nowadays, there is evidence about how gut bacteria can make us more susceptible to this pathology and affect its progression. These bacteria can produce small molecules involved in tumour growth or suppression.³ Amongst the small molecules that the bacteria produce, short-chain fatty acids are very important. These molecules are produced when the bacteria ferment the fibre we eat and have a positive effect on the gut, in particular on the intestinal mucosa. In the gut of patients with intestinal problems,

like inflammation, there is a reduction of these molecules compared with healthy individuals. Abnormal levels of these fatty acids can indicate gut microbiota dysregulation and a loss of bacterial diversity, which can trigger intestinal diseases like colorectal cancer.^{4,5}

Patients with colorectal cancer have less specific types of so-called “good bacteria”, like *Lactobacillus* and *Bifidobacterium* spp., and more that can cause inflammation, like *Escherichia* and *Klebsiella* spp. Studies analysing faeces from patients with colorectal cancer with poor sleep quality revealed an increasing amount of “bad

bacteria” while healthy individuals who reported good sleep had more “good bacteria”.⁶

We dreamed even before we had a brain

Sleep has been conserved throughout evolution. Even the most primitive animals that have a less complex brain than humans need sleep. Interestingly, since during sleep we are in our most vulnerable state, there must be something behind this behaviour that pushes all animals to risk their lives every day to sleep.⁷ Indeed, while we are sleeping, we think that everything is on pause but



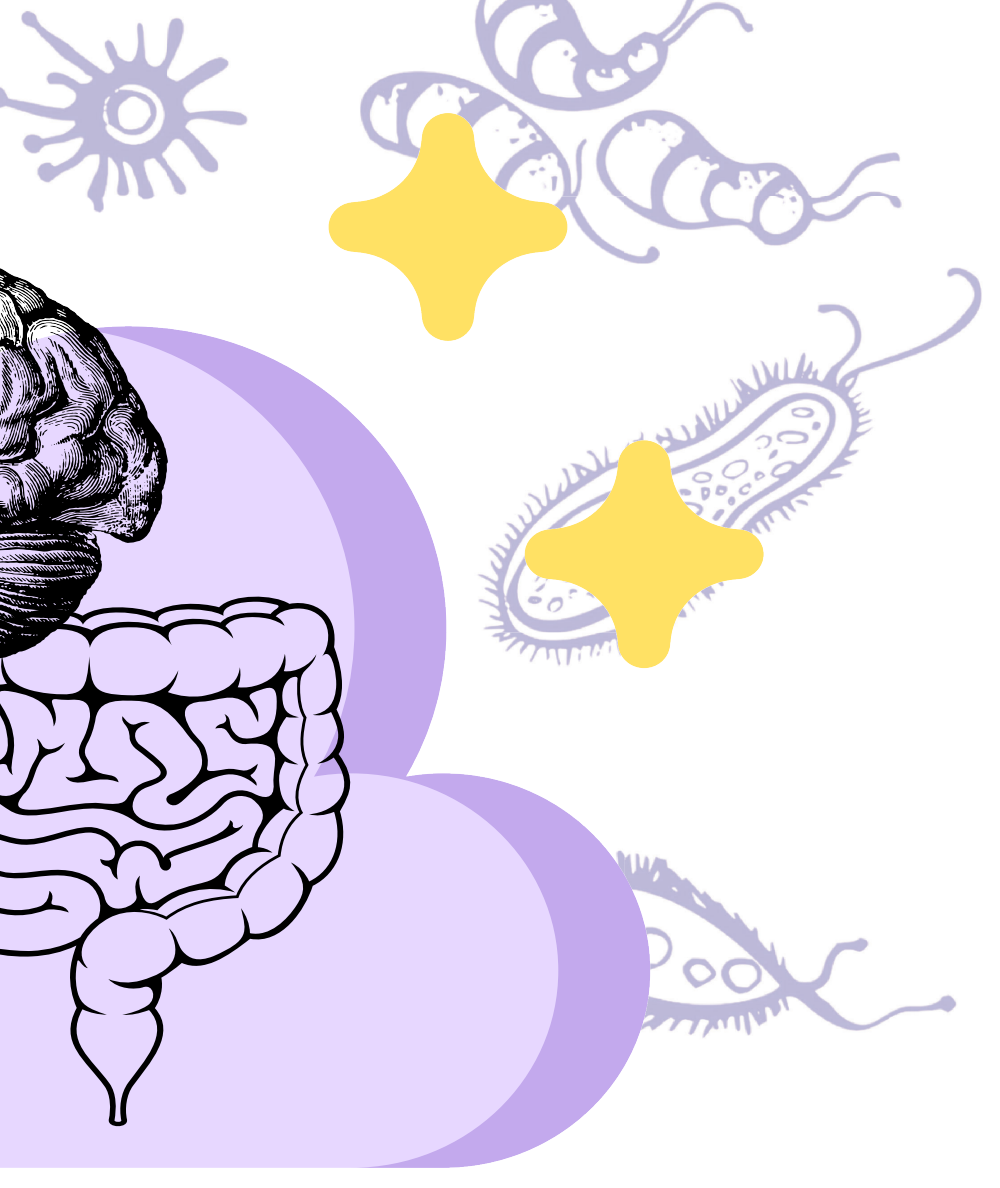
This is called the hash, pound, or number character. A hashtag is a keyword or set of keywords that is preceded by the # character. It is used in social media to create a thread of conversations around a specific theme or topic conveyed in short texts or microblogs. It is commonly used in Twitter, Instagram, YouTube, Pinterest, etc.

A dictionary of most common hashtags can be found at <https://www.hashtags.org/definition/~h/>. For your info, EMWA is compiling a list of standardised hashtags for our social media use.



This is called the “at” sign or symbol. The @ sign is part of email addresses and social media user names (“handles”). Our EMWA handles are as follows: @Official_EMWA (Twitter), @EMWA (LinkedIn), and @europeanmedicalwritersassociation (Facebook)

The two most important keys on your keyboard



a lot of things are taking place. When we are sleeping the pituitary gland in the brain releases growth hormone which helps our bodies to grow and repair. During sleep, we also consolidate what we have learned and memorised the day before.^{8,9}

How bacteria affect our sleep

Researchers in the last decade have shown that sleep is affected by external and internal cues, like circadian rhythms and feeding. Our eating habits can affect our microbiota composition and therefore the amount and type of metabolites they release. Studies in mice depleted of microbiota showed impairment of sleep associated with a drastic reduction in serotonin levels, an important regulator of sleep. Thus, microbiota imbalance can affect our sleep by altering the intestinal balance of neurotransmitters.¹⁰

Changes in the diversity of our gut bacteria can affect our intestinal function and make us more vulnerable to intestinal diseases. How can we know if something is going wrong in our gut microbiota? Because the gut communicates with the brain through the gut-brain axis – signals

coming from the microbiota can affect our behaviour. Nowadays, more studies show that by tracking our changes in mood, sleep, or eating habits, we can modify our lifestyle to improve our gut and overall health.¹¹

How can we help our bacterial community and improve our sleep?

Diet and lifestyle are important factors to achieve overall health, prevent gut disorders, and reduce the predisposition to developing more serious diseases. Eating more fibre-rich foods, vegetables, and fruits, and avoiding antibiotics when they are not needed, can help you to keep a healthy gut.¹²

Despite all the information available nowadays, further research is needed to understand the link between gut disease, microbiota, and sleep. Studies with animal models like mice and fruit flies can help researchers understand behavioural changes in the early stages of the disease. In the future, we could use sleep tracking as a diagnostic tool to detect gut dysfunction at its onset and help prevent the development of more aggressive pathologies like colorectal cancer.

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Good Writing Practice

Grammatical misagreement in voice

Active voice verb, passive voice verb

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Introduction

The distinction between the active and passive voice is that the subject acts by means of the active voice verb, and the subject is acted on by means of the passive voice verb.

The extensive usage of the passive voice in research writing probably results from a thematic subject-focused pattern (*the protein was isolated*) rather than an agent-subject focused narrative pattern (*we isolated the protein*). Such thematic focus facilitates inter-sentence continuity, because the subject can consistently be the *protein* (or an equivalent) rather than *we... we*, which becomes monotonous and egotistical.

The examples of voice misagreement are organised first according to journal article section (Experimental, Contextual) and second according to voice misagreement (active or passive).

Experimental sections

Part 1 – Materials and Methods section: Method

Example: Misagreement of active voice

Interviews focused on genetic, medical, and family history.

Revision

Interviews were focused on genetic, medical, and family history

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Notes

The usage of the active voice phrasal verb *focused on* with an abstract inanimate subject is a common distraction classifiable as a personification. Revision involves conversion into the passive voice. A classic example of personification is *this paper discusses*.

Part 2 – Materials and Methods section: materials

Example: Misagreement of passive voice

The system was consisted of six main features: user information, user profile management, query processor, SQL query generation, result refinement, and ontology management.

Revision 1

The system **consisted of** six main features: user information, user profile management, query processor, SQL query generation, result refinement, and ontology management.

Revision 2

The system comprised six main features: user information, user profile management, query processor, SQL query generation, result refinement, and ontology management.

Notes

Why does *was consisted of* sound awkward? Although *consisted of* is probably a phrasal transitive verb with the direct object *six main features*, usage of the passive voice is ungrammatical. In contrast, the active voice *consisted of* and *comprised* are grammatical.

Part 3 – Results section: results statement

Example: Misagreement of passive voice

The concentration of DHA was increased from the maternal to foetal liver.

Revision 1

DHA concentration **increased** from the maternal to foetal liver.

Revision 2

There was an **increased** DHA concentration from the maternal to foetal liver.

Notes

In the Example, it appears that the authors were responsible for the increase. That is, there is confusion reading *was increased* as a passive verb phrase or as a linking verb + adjectival past participle subject complement. The passive verb denotes an external action; the linking verb + past participle adjectival denotes an observation.

In Revision 1, usage of *increased* involves an intransitive verb. In Revision 2, the existential somewhat wordy *there is* structure is used. The shift is also from a narrative to a descriptive format, a format befitting an existential observation, which is appropriate for the Results section.

Contextual sections

Part 1 – Introduction section: Hypothesis

Example: Misagreement of active voice

β -Catenin may involve early liver development.

Revision 1

β -Catenin may **be involved in** early liver development.

Revision 2

Early liver development may involve β -Catenin.

Notes

In the Example, you can see the illogical relation conveyed by the active voice verb *involve* between the subject *β -catenin* and direct object *development*.

Revision 1 involves conversion into the passive voice; Revision 2, inversion of subject and direct object.

Summary

Despite frequent usage of the passive voice, some impeded immediate comprehension distractions do occur. Most common, particularly by ESL (English as second language) writers, is an inverse misagreement between the subject and direct object. (*β -Catenin may involve early liver development*, instead of the inverse, *β -Catenin may be involved in early liver development*). ESL misusage is also common for transitive phrasal verbs such as *consists of* which seems awkward as a passive (*was consisted of*). As yet, there seems no explanation why some verbs are ungrammatical in the passive voice.

The revisions involve changing verb voice (active to passive or passive to active) or inversion of subject and direct object to correct for active voice misagreement.

Schematised misagreement in voice – distractions and revisions

Active voice misagreement

Materials and Methods section: method (Experimental #1)*

Interviews focused on genetic, medical, and family history.

Transformation: active → passive voice

Interviews **were focused on** genetic, medical, and family history.

Introduction: hypothesis (Contextual #1)*

β -Catenin may involve early liver development.

Transformation: active → passive voice

β -Catenin may **be involved in** early liver development.

Replacement: inversion between subject and direct object

Early liver development may involve β -catenin.

Passive Voice Misagreement

Materials and Methods section: method (Experimental #2)*

The system was consisted of six main features: user information, user profile management, query processor, SQL query generation, result refinement, and ontology management.

Transformation: passive → active voice

The system **consisted of** six main features: user information, user profile management, query processor, SQL query generation, result refinement, and ontology management.

The system **comprised** six main features: user information, user profile management, query processor, SQL query generation, result refinement, and ontology management.

Results section: results statement (Experimental #3)*

The concentration of DHA was increased from the maternal to foetal liver.

Transformation: passive → active voice

The concentration of DHA **increased** from the maternal to foetal liver.

Transformation: narrative → descriptive pattern

There was an **increased** DHA concentration from the maternal to foetal liver.

*The part number in the Experimental or Contextual section

The Crofter: Sustainable Communications

Editorial

Greetings from the croft! In June, the Sustainability Special Interest Group (SUS-SIG) marked its first year of existence and we have embarked on our second year with much enthusiasm. Kate Silverthorne has written an inspiring feature article in this issue on doughnut economics and its relationship to the healthcare industry and health technology assessment. (See p. 76.) And we have two contributions for The Crofter. The first is related

to one of the SUS-SIG's founding objectives, which was to register EMWA as a UN sustainability partner organisation. *Medical Writing* Editor-in-Chief Raquel Billiones explains what this means and outlines the future activities the SUS-SIG aims to initiate and coordinate within EMWA. The second is on inclusive language by Daniela Nakagawa. I first became aware of inclusive language as a physical therapy student in the early 1990s and I thought I had a pretty good idea of what this entailed.

SECTION EDITOR



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But in reading Daniela's article, in which she discusses inclusive language and its role in mental health and sustainability, my eyes were opened, and it has given me food for thought. Speaking of food, perhaps now is a good time to grab a doughnut, sit down, and read. Enjoy!

Kimi

EMWA becomes a partner organisation in the UN Partnership for Sustainable Development Goals platform

One of the objectives of the Sustainability Special Interest Group is to register EMWA as a United Nations (UN) sustainability partner organisation in the UN global registry of voluntary commitments and multistakeholder partnerships for Sustainable Development Goals (SDGs). "The Partnership for SDGs platform is open to all stakeholders, including Member States, civil society, local authorities, private sector, scientific and technological community, academia, and others, to register a voluntary commitment or multistakeholder partnership which aims to drive the implementation of the UN 2030 Agenda and the SDGs."¹

And we did it!

After receiving endorsement from the EMWA Executive Committee on May 21, 2021, we submitted our registration on June 26, 2021.

Of the 17 SDGs, we chose the following three as our focus, which are closely related to EMWA activities:



Goal 3 – Ensure healthy lives and promote well-being for all at all ages



Goal 4 – Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all



Goal 12 – Ensure sustainable consumption and production patterns

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Then we planned for deliverables within the scope of these SDGs. These goals were to be achievable (and their achievement measurable) within the remit of EMWA's activities as a professional organisation of medical writers and communicators. (See Table 1).

The SUS-SIG will coordinate these initiatives and will work with other SIGs and entities within EMWA, including the VetSIG, the MedComms SIG, the SIG on Communication with the Public, and the Education Committee (EC). The SUS-SIG will also monitor the progress of the deliverables and provide an update to the EC and the membership.

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Table 1. EMWA deliverables as a UN SDG partner organisation

SDG	Deliverable	Specific activities	Measures of success
SDG 3	Best practice document(s) and position statement(s) on different aspects of scientific and health communications	Documents on responsible reporting, fact-checking, inclusive language, etc.	Number of documents developed, published, disseminated, and translated Social media metrics
SDG 4	Educational offerings on topics relevant to sustainability in the healthcare industry	Educational offerings (e.g., webinars, workshops, podcasts) on the regulatory requirements for environment risk assessment (ERA) of healthcare products	Number of workshops, webinars, podcasts, etc. Number of participants Geographic reach
SDG 12	Data on EMWA's carbon footprint, reduction strategies towards carbon neutrality	Examination of EMWA's conference activities, travel and reimbursement policies, contracts with vendors, etc.	Collection of baseline data on EMWA's carbon footprint Strategies for reduction and offsetting
SDG 3 and 12	Advocacy for initiatives that minimise waste of research resources and efforts, and foster public trust	Initiatives such as open access, open science, transparency, disclosure and data sharing, patient centricity, etc.	Number of webinars, seminars, symposia, journal articles, newsletters focusing on these initiatives, etc. Number of participants Social media metrics

Inclusive language: A hidden power at the hands of medical writers

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To work as medical writers and medical communicators demands adaptability and open-mindedness. From adopting new technologies to keeping up with the constant evolution of languages, we must update the tools we use and the way we work. Incorporating inclusive language in the materials we produce, that is, “language that avoids the use of certain expressions or words that might be considered to exclude particular groups of people,”¹ requires precisely that. By doing so, we contribute to alleviating the psychological and physical pain of many. This article aims to describe the impact of language; discuss the connection between inclusive language, mental health, and sustainability; and provide examples of inclusive language and resources for further reference. After reading this article, I hope you are inspired to use inclusive language in your documents, communication, and daily life. It is not an easy task but is one worthy of our effort.

Our words carry more than their literal meaning. They also convey our emotions and thoughts about something or someone. Through the language we use and how we use it, we transmit what we consciously or unconsciously

think and feel.³ Words and ways of communicating that we learned from social and cultural experience⁴ express both their explicit meaning and stereotypes and biases associated with “undesirable” features in others. They are our tools to communicate but also a repository of our prejudices.⁵ Through them, we reduce those carrying these features “from a whole and usual person to a tainted, discounted one.”⁶ Words such as *non-white, disadvantaged, the poor, real woman, bossy, non-straight, the elderly, wheelchair-bound or normal*, encode our thoughts about traits we must reject. When choosing a verb over another or the passive over the active voice, we influence who or what we attribute causality and social responsibilities to and reinforce discriminatory power structures.⁷ By using certain words, verbs and voices in everyday-life communications, we normalise, make routine, and support discriminating behaviours, whether we are aware of this or not.

But words can also carry our explicit intention to include others. With inclusive language, we treat everyone as equal and with respect. Inclusive language is a positive alternative to sexist, racist, biased, discriminatory, and stigma-

tising language that alienates the person we address. It counteracts language-based discriminatory patterns; for example, by replacing *non-white* with terms such as *people of colour, Black or Brown*, we acknowledge and validate people who are not white.

Failing to communicate inclusively alienates those who would otherwise participate in all society’s affairs. It excludes them because it is hostile and offensive, and when offended at work, in a doctor’s appointment, or among colleagues, who would want to participate? Unfortunately, the effects of discriminatory language go beyond not visiting a biased physician or not engaging with sexist colleagues. Racist verbal abuse, for example, is related to a higher chance of dying prematurely, having a respiratory illness, high blood pressure, depression and anxiety, stress, anger, psychosis, and feeling suicidal.^{8–10} Moreover, underlying non-inclusive language are prejudices that those in charge translate into life-altering policies, decisions, and behaviours. For

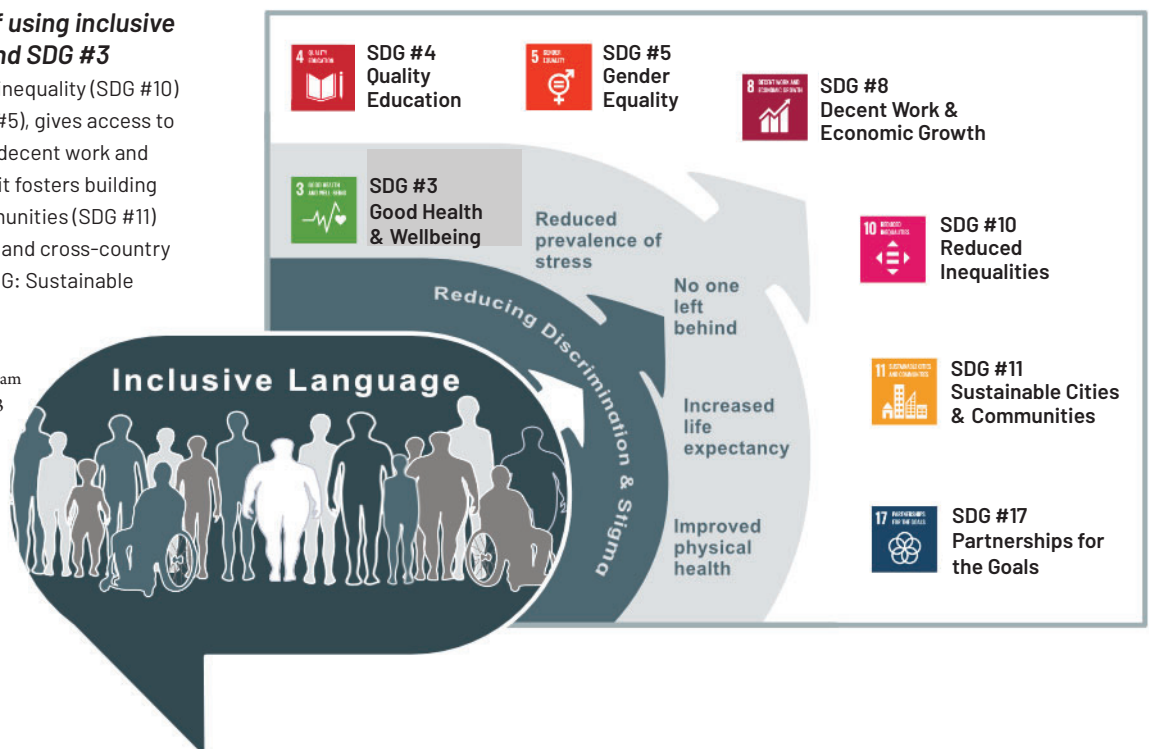
“Use language to describe, not to label.”

Elle Graham-Dixon²

Figure 1. The effects of using inclusive language spread beyond SDG #3

Inclusive language reduces inequality (SDG #10) and gender inequality (SDG #5), gives access to quality education (SDG #4), decent work and economic growth (SDG #8), it fosters building sustainable cities and communities (SDG #11) and facilitates cross-sector and cross-country collaborations (SDG #17). SDG: Sustainable Development Goal.

Figure created by EMWA’s graphic team based on Figure 1 in this reference.²³



example, lower access to healthcare services and economic, political, social, and psychological processes cause health disparities^a among different social groups.¹³⁻¹⁸ The members of these groups have, in consequence, worse physical and mental health than those belonging to socially advantaged sections of society.

The role of inclusive language in mental health and sustainability

In 2015, the United Nations (UN) included mental health in the 2030 Agenda for Sustainable Development and the Sustainable Development Goals (SDGs).¹⁹ Specifically, it was incorporated within SDG #3, which aims to “ensure healthy lives and promote wellbeing for all at all ages” by providing universal health coverage, including access to mental health treatment.

But despite this critical step forward, the World Health Organization (WHO) Commission acknowledges that access to mental health treatment by itself will not relieve the world from the burden of mental disorders unless authorities address their causes: the adverse social conditions under which people live.^{20,21} People in which some factors combine, such as belonging to a particular ethnicity, gender, age, income group, and education level, among others, are at an increased risk of having a mental health condition than those who do not share these life circumstances or characteristics.^{22,23} Tackling these adversities is imperative if the UN is serious in fulfilling its commitment to SDG #3 because “social determinants are ‘the causes of the causes’ of ill health, including mental ill health.”²²

Discrimination is, among others, one of the social adversities the WHO identifies as a determinant of mental disorders and a cause of physical illness.²² Like other social determinants of mental health, discrimination harms us through the body’s stress response, which over time, negatively affects our psychology and physiology.²⁴ Members of a marginalised group (i.e. minority ethnicities and nationalities,

Discrimination is, among others, one of the social adversities the WHO identifies as a determinant of mental disorders and a cause of physical illness.

migrants, younger and older people, differently-abled persons, people with obesity, the LGBTQIA+ community, individuals without homes, and persons experiencing a medical ailment) are at risk of having mental health conditions in response to the discrimination they face every day.²⁵⁻²⁸ To add insult to injury, those with mental disorders also experience stigma and discrimination, exacerbating their conditions.²⁹

Given that discrimination causes mental health problems, and non-inclusive language transmits the stereotypes, stigmas, and biases by which we discriminate, using this language could perpetuate mental health problems in the population it targets. Inclusive language is a preventive way to take care of people’s mental health. As medical writers and medical communicators, we are in a prime position to demonstrate and promote inclusive language in the documents and visuals we create and in our interactions with others. By doing so, we contribute to making SDG #3 a reality and simultaneously fulfilling the aims of other SDGs (see Figure 1).

Using inclusive words

According to the Linguistic Society of America (LSA), “inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities.”³⁰ In their *Guidelines for Inclusive Language*, the LSA describe its basic principles:^b

- It does not stereotype individuals based on their group membership (e.g. “Asians are good at maths”).
- It does not reference normativity, normality, or any standardised behaviour or way of being (e.g. *transsexual and normal people*).
- It does not use descriptive euphemisms (e.g. *differently-abled*).
- It uses updated names for countries, professions, languages, and ethnicities (e.g., *high-, low- or middle-income country* instead of *first-, second- or third-world country*).
- It avoids the passive voice if it places individuals as the objects of others or if it

allows the subject not to be held accountable for their actions (e.g. “She was beaten”).⁷

- It encourages using gender-neutral pronouns (*they, one* instead of *he, she*) and plural noun forms (e.g., *people, individuals* or *humanity* rather than *men* or *mankind*) and avoiding terms marked for masculine gender (e.g. *Congressman, mailman, fireman, and policeman*; use instead *Member of Congress, mail clerk, firefighter, and police officer*).
- It adds gender-specific modifiers (e.g. *male nurse* instead of *nurse*) or not (e.g. *boss* instead of *female boss*) to avoid the inference that the unmodified terms “only apply fully to those whose gender is not specified by the modifier.”
- It uses person-first languages, which, as the term implies, refers first to the individual and secondly to the disability (e.g. “Pat is a person with schizophrenia” or “Pat has schizophrenia” rather than “Pat is schizophrenic” or “Pat is a schizophrenic person”).^{31,32}

Table 1 overleaf intends to provide you with some examples of inclusive terms. We invite you to incorporate them into your professional and personal life and keep yourself updated on this topic (go to the “To know more” section for more sources).

The power of sustainable communication

When we alienate people through our words and the way we use language, we all lose. Those alienated lose representation and suffer, and those already represented miss the benefits of diversity and people’s diverse lived experiences. By using inclusive language across our work, medical writers and medical communicators show people, such as patients and clinical trial volunteers, that they matter and that we care. We also pave the way for those in charge, like practitioners and regulators,

to treat others with respect and dignity. Words can either dehumanise or transmit that we are committed to building an egalitarian society where everybody has access to all it can provide: education, healthcare, employment, freedom of movement, housing, and in a more abstract way, acceptance, validation, and love.

Languages constantly change, evolve, and adapt to the times. They are living entities. This also holds for inclusive language.

To know more

Languages constantly change, evolve, and adapt to the times. They are living entities. This also

^a Also called *health inequalities*, the term refers to “systematic variations in the mental or physical well-being of members of different social groups that specifically result from inequitable economic, political, social, and psychological processes.”^{11,12}

^b Most of items in the list are taken from the LSA’s guidelines, otherwise it will be referenced.

Table 1. A nonexhaustive list of noninclusive terms and their more inclusive counterparts

Non-inclusive	Inclusive
Ethnicity, race, and nationality	
Afro-American, coloured, Negro	African, African American, Black
American	U.S. citizen, a person from the US.
Asians/Oriental	People of Asian/Southeast Asian descent, Asian American, or specify by nationality
Caucasian	White people
First World/Third World (country)	high-, low- and middle-income countries (LICs, MICs, LMICs)
gypsy, gyp/gip	Romani
Hispanic	use person's country of origin or nationality
mixed, mixed-race/blood/heritage, half, mulatto	biracial, multiracial
non-white, coloured	people of colour, minority
Sex and sexuality	
biological/born female, female-bodied	assigned female at birth (AFAB)
biological/born male, male-bodied	assigned male at birth (AMAB)
female-to-male (FTM)	transgender man
homosexual, non-straight	men who have sex with men, women who have sex with women (for behaviour) gay, lesbian, bisexual, pansexual, asexual, queer (for identity)
male-to-female (MTF)	transgender woman
sexual preference/identity, lifestyle choice	sexual orientation
transgender people and normal people	transgender people and cisgender people
Gender equality	
both genders, opposite sexes	all genders
gender non-conforming/neutral	gender non-binary
guys, girls, gals	everyone, all
husband, wife	spouse, partner
ladies and gentlemen	everyone, folks, honoured guests
mother, father	parent
Health	
able-bodied	non-disabled, enabled, "... does not have a disability"
addict, drug abuser/addict	someone experiencing/with a drug problem/addiction
birth defect	a person with a congenital disability/birth anomaly
clean/dirty test results	negative/positive test for drugs
die of/from AIDS	die from an AIDS-related illness/complications from AIDS
Cancer patient	a person with (type) cancer
Down's person	a person with Down Syndrome
drug abuse	drug misuse
an/the epileptic	a person with epilepsy/seizure disorder
a handicapped person, the handicapped/disabled/ deafblind, a/the paraplegic/quadruplegic	a person with (physical) disabilities/who is deafblind, a person with a spinal cord injury/ paraplegia, a person who is paralysed
HIV-positive person/people	person/people living with HIV
junkie	someone who misuses heroin
mental illness	mental health condition
mental retardation	intellectual/developmental disability
mute	a person who cannot speak/has difficulty speaking/uses synthetic speech/is non-vocal/non-verbal
senile/demented	a person with Alzheimer's disease/dementia, a person who has dementia
serostatus, seropositive, serodiscordant (a couple in which one member has HIV and the other does not)	HIV status, HIV positive, mixed-status
wheelchair-bound, confined to a wheelchair	wheelchair user
you are/suffer from (condition)	you have/live with (condition)



Non-inclusive

Inclusive

Appearance

dwarf, midget	person of short stature, little person
the obese	ask ^a

Age

nursing home	care centre
the elderly, the aged, seniors, geriatric (people)	older adults, older people, ages xx and older

Socioeconomic status

at -risk, needy, disadvantaged	people with low income
the homeless	people experiencing homelessness/who are homeless/houseless
the poor	people experiencing poverty

Science

Blacklist to list problematic entities	excluded list, denylist
Whitelist to list good, trustworthy entities	included list, allowlist, safelist

^a The discussion is still ongoing. Some activists are reclaiming the word “fat” instead of more euphemistic adjectives like big, large, or curvy.⁴³

holds for inclusive language. There is a continuous debate about what is offensive and what is not. Some terms that used to be offensive, like calling someone “queer”, have been reclaimed by activists. We encourage you to (re-)visit these sources of information to keep up with the latest updates.

- American Medical Association (AMA) Manual of Style⁴⁴
- American Psychological Association (APA) Bias-free language guidelines⁴⁵
- Conscious Style Guide⁴⁶
- Diversity Style Guide³⁴
- LGBTQIA+ Glossary of Terms for Health Care Teams⁴⁷
- Linguistic Society of America (LSA) Guidelines for Inclusive Language³⁰

We also invite you to see these documentaries about mental health and the role that stigma plays in it:

- *The Me You Can't See*⁴⁸
- *The Wisdom of Trauma*⁴⁹

And finally, there is writing assistant software that can assist you in writing inclusively:

- Grammarly identifies offensive and non-inclusive words and expressions and offers a more inclusive alternative.⁵⁰
- Microsoft Word's Editor: “Editor's inclusive language critique offers suggestions to replace language that may perpetuate biases around age, ability, gender, sexual orientation, religion, ethnic or racial slurs, as well as outdated or sensitive geopolitical references.”⁵¹
- PerfectIt allows you to identify and eliminate words and phrases that might need consideration.⁵²

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Conflicts of interest

The author declares no conflicts of interest.

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Out On Our Own

Editorial

I've said it time and time again, and our author reiterates it, everyone's journey into medical writing is unique. We come from all walks of life, having gained a variety of diplomas and degrees, developed skills in academia, industry, NGOs, or start-ups, with specialisations in all different disciplines of medical, scientific, and

veterinary fields. In this issue we hear the voyage that Heather Mason has taken to get into freelancing. She has a wealth of experience under her belt, and she sparks so many relatable scenarios that many of us already in freelancing can identify with. She leaves us inspired and reassured that with some focus and self-confidence (don't let that imposter syndrome set

in), we can achieve our dreams and goals in the somewhat isolating world of freelancing.

I hope to see many freelancers at the Freelance Business Forum in November, so we can socialise and share more experiences and knowledge with each other.

Stay safe.

Laura A Kehoe, PhD

Freelancing: Freedom or isolation?

I realise that every step of my varied work and personal life has tailored my particular uniqueness, leading me to where I am sitting today, a British ex-patriot living in the foothills of the Pyrenées in Southwest France.

Let's face it, we are all unique. The route into medical writing is a wide and varied one. I can confidently say that each story has been different from the many medical writers I now know. There is definitely no convention.

Even once you have arrived in the field of medical writing, in the words of Sheryl Crow, "Everyday is a winding road". So, where did it all begin for me?

If I can choose the most significant lesson in this journey with you, it would be to never listen to others regarding your capabilities of reaching a goal. For too many years, I took too much notice of those telling me what I would not achieve or what I was not capable of, rather than listening to my intuition. Should I have had adequate self-belief, I would have been a veterinary surgeon today and not a medical writer.

So, early on, I became a veterinary nurse rather than continuing my dream of being a vet. After I qualified, I was never given any real responsibilities that my qualifications had prepared me for. I was still limited to cleaning kennels, answering the telephone, and being a general dogsbody (forgive the pun).

Disillusioned, I decided to leave a job that had been a joy to me and became a laboratory assistant in an agricultural research institute. This was the next best thing: Milking cows, growing microbes from their milk, and learning about vaccines. I loved it, and my passion for science was born.

My personality is not one for being static. I am always looking for something new. I don't sit still, metaphorically speaking. So, while still working, I completed a part-time biomedical sciences diploma. I was inspired by the colleagues around me, their level of knowledge, and their enthusiasm for the day job. Before the end of my part-time studies, it was obvious that I had to pursue a degree to have any hope of furthering my career. So, after 3 years, I left for university in the wet and warm Southwest of England to complete a degree in biological sciences.

When I graduated and returned to the family home, the obvious place to start job hunting was to go back to the research institute I had left 3 years previously. Many of my ex-colleagues at the research institute had become friends, so it was an easy transition back into working life. In fact, there was a new research facility being set up concerned with producing a vaccine for the human immunodeficiency virus (HIV). I was lucky enough to secure the role of laboratory manager. I was tasked with ordering new equipment and consumables, learning about category four level of biocontainment, and even having responsibility for my own research project.

Once the laboratory was functioning as it should, and I had some good results, I started to get an itch to pursue a PhD. It seemed as though everyone else around me had one, and that is what I needed to get to the next step in my career. I accepted a PhD position at the University of Wales, College of Medicine, in Cardiff, UK, researching the role of the immune system in rheumatoid arthritis.



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This proved to be the greatest professional challenge of my life. It was a shock to my system. I thought that a PhD would be really getting deep into the science, thinking of ways around negative results, pursuing a research path that was new and unique. In fact, for the first 2 years, it was none of those things. It was clear that this PhD programme was a cheaper way to get a research assistant. I found myself completely restricted in all the lateral and investigative thinking skills that I had picked up in my previous roles. I was simply told what I was doing and how I was going to do it. However, I don't give up easily. There were so many times I wanted to walk away, but I was worried about what my family would think, and I had no idea what alternative career path I could go down. I was also now a homeowner, so I had responsibilities.

Finally, after 2 years of not achieving any significant results and pretty much no material for my thesis, it was agreed that I could try things my way for a bit. I cannot tell you what a relief it was. All the things that I had suggested at the beginning of the project were now being taken seriously. I quickly started to get results. I worked so hard in that final year, so determined to have enough material to make the years of mental torture and frustration worthwhile.

Unfortunately, those 3 years killed any



enthusiasm I had for laboratory work. Two whole years of doing the same types of experiments day in day out were soul-destroying. By the project's third and final year, I had no idea what I wanted to do with my career. Luckily, someone came to the office one day, and they said they were a clinical research associate (CRA). He explained what the day job meant, and it sounded perfect! So that was the route I went down. At that point, without experience, it was tough to get a CRA position. So, I started a medical affairs role in a pharmaceutical company presenting clinical trial data to healthcare professionals. It was the foot in the door to the pharmaceutical industry that I needed to finally become a CRA.

I loved being a CRA. The work was varied, and I spent several days a week out and about meeting people. I made use of my interrogative brain, and it was also rewarding to see the positive effect of the investigational drug. I worked on projects studying many different therapeutic areas throughout my CRA life, some of which have made a massive difference to people with rheumatoid arthritis and those with

cystic fibrosis. I worked as a CRA for 8 years, finally becoming freelance, allowing me to have more flexibility.

During my CRA career, I became a mum for the first time. Travelling and long hours were no longer a sensible option with a baby, especially as he has additional needs. So, I took a few months off and found a position working as a medical affairs specialist in the rare disease group of a pharmaceutical company. It was a short-term contract to cover a notice period for the person already hired for the full-time job. However, the team was a really nice group of people, and at the end of the contract, my line manager wanted me to stay, offering me a newly created role of scientific communications specialist. The bulk of my work was to write newsletters on recently published material for

each of the rare diseases, sales and marketing documents, liaising with physicians who were undertaking their own research, bespoke literature reviews, and writing posters for conferences. They were my sole client for 4 years until there was a company restructure, the team was disbanded, and around the same time,

Finally, after 2 years of not achieving any significant results and pretty much no material for my thesis, it was agreed that I could try things my way for a bit. I cannot tell you what a relief it was.

I moved to France for a new life.

I had a period of time out of work when we moved to France. I had 12 months of maternity leave and then a further 18 months of searching for new work. Although I didn't think a career break would be a deal-breaker, it was for all recruitment agencies that I tried. Of course, I understood that people currently holding a medical writing position were more up to date than I was. I applied for very junior positions, both as a CRA or as a medical writer, but I was told that I was either overqualified and wouldn't stay in the post or had been out of the industry too long. I began to think that I would never be able to get a writing job again as I would never fit the criteria they were looking for.

Then, slowly, things started to move. I decided to set up Coufetry Comms, and rather than rely on recruitment agencies, I drove myself, I became my own advocate. Since starting medical writing, I can honestly say that I have never gained a contract through a recruitment agency. I'm telling this story not at all to be disparaging to those agencies, but to simply say that if you are struggling, do not feel that you need to rely on them. I am proof that you do not.

I learnt how to set up a website, something very easy to many I know, but not for me at that stage. I became more active on social media, and I reached out to colleagues from my past.



In the words of Benjamin Franklin, American printer, publisher, author, inventor, scientist, and diplomat: “Energy and persistence conquer all things”.

Then by chance, I answered a post from someone on LinkedIn who had been through a similar experience. It was a different industry to my own, but they had held down the same position for 30 years and were then made redundant. As they found themselves competing in a marketplace full of younger candidates, they were told that their salary expectations would be too high as they had too much experience. For the more junior positions, they were told that they had too much experience. It resonated so much with me that I replied to him with empathy.

That single reply opened the door ajar for my first role in my new life. A medical writing company from Japan contacted me to say that they would be happy to give me a trial. I had won my first contract, conducting literature reviews.

The next break came when someone replied to a post I had put on a local Facebook group, asking whether there were any pharmaceutical companies or writing opportunities in the area. They suggested that I join the European Medical Writers Association. I attended my first conference in Warsaw, which was a very fruitful decision. I secured another contract, providing daily summaries for an educational platform for healthcare professionals.

At this same conference, I got chatting with a person sitting beside me in a workshop. We found out that their father-in-law was the paediatric consultant I had

previously worked with during my time in the rare disease group. It had finally come full-circle. Soon afterwards, I had a call from them inviting me to join a very exciting paediatric rare disease project, writing patient treatment and management guidelines. This has been two years in the making, and I am proud to say they were recently published.

Since Warsaw, I have attended other EMWA conferences where I have met people I now consider friends, and we have helped each other out when it comes to finding work.

The snowball continues to grow as it rolls. After only 3 years since its conception, I now have an established business that continues to expand, with repeat business and new clients regularly coming to me. I am learning new therapeutic areas, I am comfortable knowing what I am good at, what interests me, and the direction I would like my business to take.

The moral of my story is to believe in yourself, don't be swayed by other people's ideas of your capabilities, and be your own advocate. I have learnt invaluable lessons about myself during this convoluted career path. I have felt isolated at times, without a mentor or a line manager to guide me, but this has meant that I have gained skills of persistence, diligence, and flexibility. If one route doesn't work, I WILL find another.



Being out on our own requires skills beyond that of writing alone. While it gives us the freedom to choose our path, if allowed, a feeling of isolation can creep in, especially in the early days. This is when it's wise to connect with other medical writers, discuss new avenues, set up new local groups, anything to keep the isolation demons at bay. We must be masters of our destiny.

In the words of Benjamin Franklin, American printer, publisher, author, inventor, scientist, and diplomat: “Energy and persistence conquer all things”.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by EMWA.

Conflicts of interest

The author is the proprietor of Coufetry Comms and declares no conflicts of interest.

Author information

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Upcoming issues of **Medical Writing**



December 2021:

Medical journalism

We are living at a time when the general public is increasingly interested in scientific and medical advances. Hence, for medical writers, understanding our audiences and how to efficiently reach them is key. This issue will cover those insights.

Guest Editors: Evguenia Alechine and Phil Leventhal

The deadline for submitting feature articles has passed.



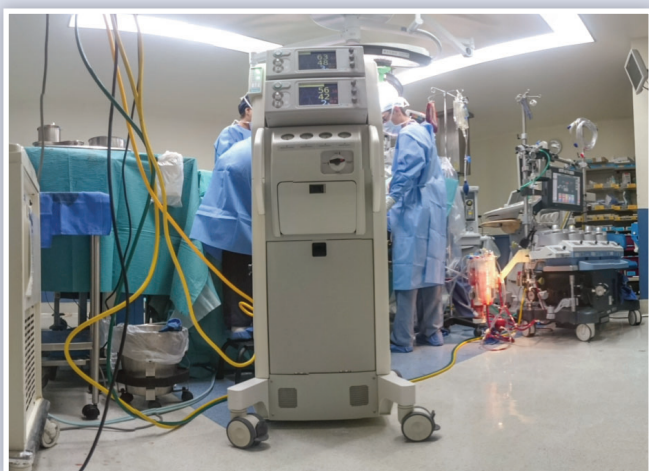
March 2022:

Sustainable communications

Sustainability is a key focus area across all economic sectors, including the pharmaceutical and healthcare industry. This issue will focus on where and how scientific and medical writing can contribute to current debates on scientific and environmental problems and their impact on human health. The issue will also cover emerging career opportunities for medical writers in this area.

Guest Editors: Surayya Taranum and Elisa Sala

The deadline for submitting feature articles is December 1, 2021.



June 2022:

Medical devices

The implementation date of the EU Medical Device Regulation has arrived, marking a new era of heightened attention to medical device safety and performance. This issue will explore the experiences, challenges, and lessons learned over the last years preparing for the MDR requirements as well as potential opportunities these changes bring. Moreover, we touch base on the implementation of the EU In-Vitro Diagnostic Regulation and on other aspects of writing for medical devices.

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The deadline for feature articles is March 1, 2022.

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



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