Medical Writing

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Volume 34 Number 1 | **March 2025**

EMWA EUROPEAN MEDICAL WRITERS ASSOCIATION

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

Medical Writing

THIS ISSUE **March 2025** | Volume 34 Number 1

Rare Diseases

"To all people out there with rare diseases, this issue is dedicated to you."

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Rare diseases

doi: 10.56012/nvvg4559

Medical writers are vital partners in raising awareness of rare diseases and advancing research.

Rare diseases affect around 1 in ten people, or an estimated 300 million people globally, with over 7,000 rare conditions. National definitions of a rare disease vary from a prevalence of 5 to 80 per 100,000 population. Due to low prevalence and lack of knowledge in the healthcare profession, this community often has a long journey to diagnosis, termed the "diagnostic odyssey", or even has several misdiagnoses along the way.

The zebra is the symbol that represents rare diseases. This originates from a quote from an American physician, Dr Theodore Woodward: "When you hear hoofbeats, think horses, not zebras". He taught medical students to think of more common conditions before the rare diagnosis. Thankfully, new rare disease training initiatives in medical schools and continued professional development programmes are beginning to change this. They emphasise that rare diseases are common, and rare diagnoses should always be considered.

In the complex landscape of rare diseases, medical writers serve as crucial gatekeepers of information between science, healthcare professionals, and patients. There are unique challenges for communicating about rare diseases. The terminology is often complex, with limited research, data from small clinical trials, or case studies. Our role is synthesising information from diverse sources, including clinical trials, patient-reported outcomes, and, where available, patient registries and real-world data.

There are unique challenges when communicating about rare diseases.

However, our profession's contribution to rare disease research and patient care extends far beyond document preparation. We require a particular set of skills, including emotional intelligence and the ability to understand the patient's perspective.

We become essential partners in advancing knowledge and raising awareness and hope for rare disease communities. We must also be familiar with communicating with diverse stakeholders, including regulatory bodies, pharmaceutical representatives, payers, and patient organisations. We could argue that medical writers who write in the field of rare diseases focus on patient-first priorities more than any other medical writing discipline.

Regulatory approval for rare disease treatments poses a unique set of challenges. We must develop expertise in emerging regulatory pathways specific to rare diseases and embrace new information technology to communicate

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complex data. Crafting narratives to present evidence from much smaller data sets and often alternative study designs can significantly impact the success of rare disease drug applications.

About 80% of rare diseases have a genetic origin, and about half affect children. Therefore, other demands in writing for the rare disease population include crafting text to present information in a way that must be accessible to children, those with cognitive difficulties, or those who may be neurodivergent. Thus, as medical writers, we must be mindful of the audience and write with ethics and inclusivity in mind. We balance scientific accuracy with clarity.

Information can be scarce and complex; developing patient education materials, informed assent and consent documents, and lay summaries empowers patients and their families to make informed decisions. There is often an under-recognised impact on rare disease research and patient care. We must continue to evolve our skills to meet the ever-changing landscape of rare disease research.

First and foremost, we wanted to recognise the incredible rare disease community. Through necessity rather than choice, the patients and caregivers become experts in their condition, and yet, so often, their voices are silenced. In an honest and open patient interview, **Richard Farquhar** talks about the day-to-day challenges of living with a rare disease, how the community can help, and what he hopes for in the future.

Designing and executing a trial in rare diseases is full of predictable and unforeseen quandaries. From the identification of study endpoints and

Author information

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Heather L. Mason is a freelance medical writer with over 14 years of experience, specialising in rare diseases and specifically inborn errors of metabolism. She also has a passion for patient advocacy and inclusion.

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

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limited patient population to finding investigators, **Bregje Mommaas, Mary H. Ryan, and Neha Agarwal** discuss the impact these have on studies and how they impact regulatory writers directly and indirectly.

An interview with **Kelley Hill** discusses the unique challenges and potential solutions when writing regulatory documents for rare disease indications for Europe and the United States.

Understanding the regional requirements for regulatory documents is also challenging, particularly in orphan drug development. **Katie Brooks, Pauline Haleux, and Montserrat Cuadrado** provide an overview of regional requirements for orphan drug applications and summarise considerations from the pre- to post-approval stages, emphasising the fundamental role of multifunctional collaboration throughout the process.

Writing clinical trial protocols for rare disease trials also offers unique demands and can often be extremely complex, time-consuming, and burdensome. **Philip Burridge** and **Julie Eastgate** describe an innovative approach using master- and sub-protocols to promote efficiency in the clinical investigation process and provide clarity to both study investigators and regulatory reviewers.

In recent years, model-informed drug development (MIDD) has come to the forefront, especially in rare diseases in children where data is scant. In an article by **Natalie Brine, Clare Dyer, and Kelly Smith**, the emerging role of MIDD in drug development and assessment is introduced. As the use of MIDD grows, the authors describe the importance of regulatory writers learning how to understand these outputs to facilitate translation into clear, strategically messaged, and impactful statements.

Ensuring population diversity in clinical trials is crucial but difficult to achieve, especially for rare diseases. **Cheryl Roberts** discusses the evolving regulatory framework aimed at encouraging diversity, the unique challenges in the rare disease landscape, and sustainable solutions. Regulatory guidelines emphasise the need for diverse participant representation, but implementation is complex due to small, dispersed populations. Strategies like adaptive trial designs, community engagement, and decentralised trials can help increase diversity. However, recent federal changes in the US raise concerns about the commitment to diversity and health equity in clinical trials.

The ultimate goals are to reduce the current challenges around diagnosis time, approve new therapies, and improve understanding of rare diseases' impact on healthcare systems.

The potential of real-world data (RWD) and patient registries in addressing research and knowledge gaps in rare diseases is discussed in an article by **Sara E. Mole, Emily Gardner, and Heather Mason**. It highlights the importance of early diagnosis, understanding disease mechanisms, and developing effective treatments. RWD, collected from various sources, including patient registries, can provide valuable insights into disease prevalence, natural history, and treatment outcomes. They also emphasise the benefits of patient registries in gathering comprehensive data, supporting clinical trials, and improving patient care. It advocates for the integration of RWD and digital health technologies to enhance research and treatment for rare diseases.

Chris J. Hendriksz, a medical doctor and Chief Community Impact Officer for A Rare Cause, shares his journey in medical writing for rare diseases. After his own child was diagnosed with a rare disease, he became an expert in inborn errors of metabolism. He describes his experience collaborating with medical writers and their essential perspectives in creating patient-friendly communications and supporting rare disease management. MWs play a crucial role in bridging gaps between patients, clinicians, and pharmaceutical industries, especially in low- and middle-income countries. Hendriksz calls for greater social responsibility and collaboration to support rare disease communities.

Roseline Favresse, the Research Policy and Initiatives Director at European Organisation for Rare Diseases (EURORDIS), discusses the rare disease landscape in Europe. EURORDIS represents over 1000 rare disease patient organisations in 74 countries, aiming to improve the lives of 30 million people with rare diseases. The European Rare Disease Research Alliance (ERDERA), a new alliance, aims to address research and funding gaps with a €380 million budget. The ultimate goals are to reduce the current challenges around diagnosis time, approve new therapies, and improve understanding of rare diseases' impact on healthcare systems. Advocacy for an EU Action Plan and a World Health Assembly Resolution is ongoing.

Judit Mészáros/EMWA Creative Team

About Nora Patterson, our cover artist

A few months ago, the Guest Editors of this issue of *Medical Writing* posted a call for young artists with rare diseases or their siblings to submit artwork to be considered for the cover. We are delighted to present the work of 17-year-old Nora Patterson of Reston, Virginia. On the cover, you will see her painting, "The Beach". On this page, you will also see another textile work that she created.

Nora has juvenile Batten disease (also referred to as CLN3 disease), a neurodegenerative condition that leads to blindness and cognitive decline, among other issues. Her earliest symptom was diminished vision at 7 years old. By the age of 14, only the perception of light remained for her. Because of her vision loss, teachers at her school assist her as needed in an art class for both high-needs and traditional students. When she works with clay, she is able to work quite independently.

"When Nora works with paint, she understands the basic orientation of the canvas and is able to apply the color she requests on the general area that aligns with her concept for the piece," according to her father, James Patterson. The yellow paint at the bottom of her work has sand in it, so it has a tactile element to it when it dries.

"Nora has always been interested in arts and crafts," her father wrote. "Today, her greatest joy in the world is making art."

From the Editor

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doi: 10.56012/rkrh4645

Rare experiences

My first experience with rare diseases was about 10 years ago, while working on a marketing authorisation for a gene therapy for a rare form of congenital blindness. We used the same regulatory guidances and document templates (i.e. ICHE3, ICHM4) like any other submission. What made this experience different were the trial participants – visually impaired children as young as 3 years old.

Clinical researchers on the Sponsor side do not get to know the participants in a clinical trial. It is part of the ethical and regulatory standards to protect patients and the integrity of the trial. But in a clinical trial of 12 participants, anonymity was difficult to keep. The participant was more than just an ID number on a form. They were very real kids. And I was a mother.

Sometimes we may inadvertently get to know our patients through many different channels, such as personal testimonials on TV shows and social media. Over the years, I got to see how those visually impaired children grew up and led normal, or even extraordinary lives, be it riding a bike, getting a driver's license, seeing a rainbow, or participating in America's Got Talent.[1,2]

It was just another job. We were not supposed to get emotionally attached to a project. But when I started writing those individual patient narratives based on audiovisual testimonials "*Yes, I can see the star, Mom!*", detachment went out of the window. And the requirement of at least 15 years of follow up[3] made it hard to completely forget these extraordinary subjects and move on.

It may sound banal, but that was the most rewarding (not financially, but emotionally) medical writing project I have ever worked on.

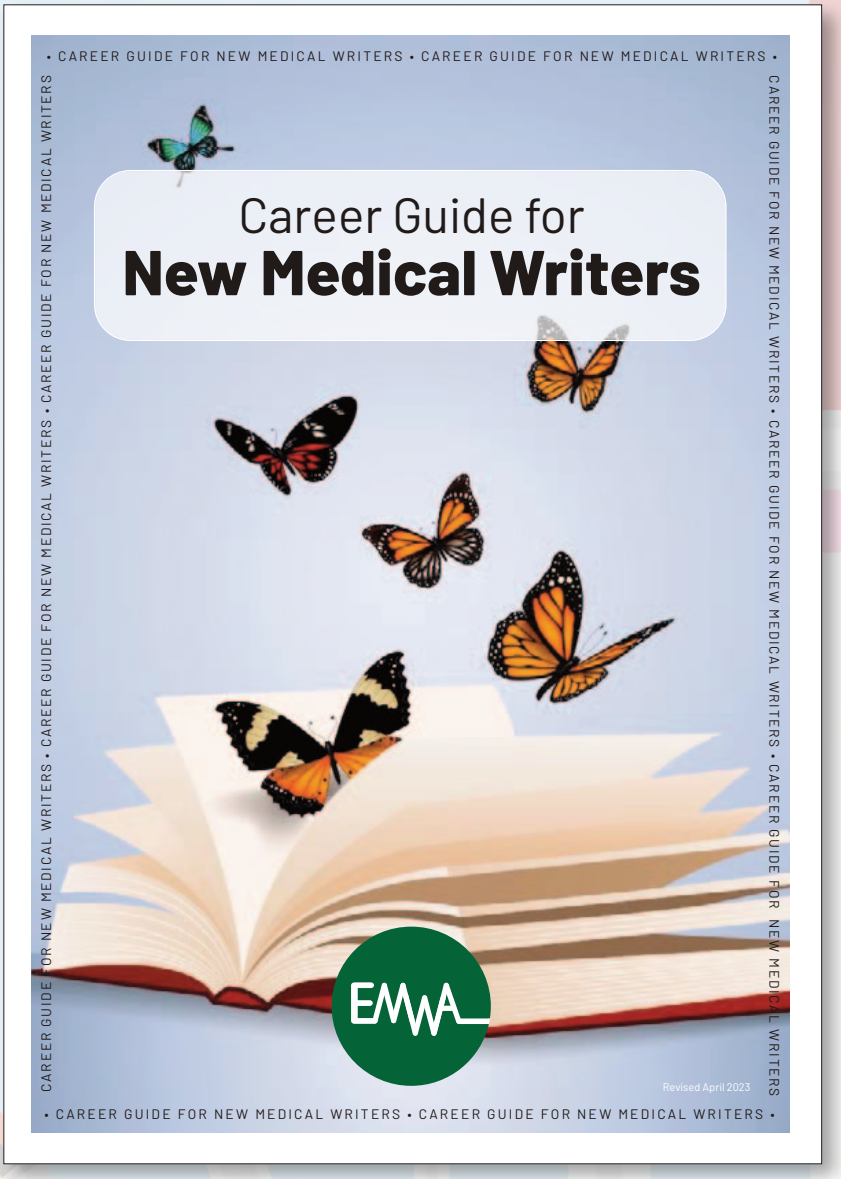
Many years later, I moved on to work for a rare disease company and personally met other rare disease patients and their families. I also had learned about orphans and zebras (see p. 51) and regularly celebrate Rare Disease Day on the last day of February.

My heartfelt thanks to Heather Mason and Sarah Milner for taking on the task of compiling this issue. Thank you to all our contributors who shared their rare experiences. And to people out there with rare diseases – this issue is dedicated to you.

Observing Rare Disease Day on February 28, 2025

References

1. Creed's Story: Seeing A Rainbow. Available from: https://www.youtube.com/watch?v=Jd40tbaTULk
2. Gene Therapy Restores Sight for Blind Patients with Hereditary Eye Disease. Available from: https://www.youtube.com/watch?v=LTWqFEOsmAk
3. US FDA. Long term follow-up after administration of human gene therapy products; Guidance for industry, January 2020. Available from: https://www.fda.gov/media/113768/download



Career Guide for New Medical Writers

EMWA's Getting into Medical Writing group has created an updated *Career Guide for New Medical Writers*, which is available on the EMWA website. If you're new to medical writing, it's a useful resource that will help you take your first steps on this rewarding career path. You can email us at gettingintoMW@emwa.org with comments.

President's Message

Writing for rare diseases

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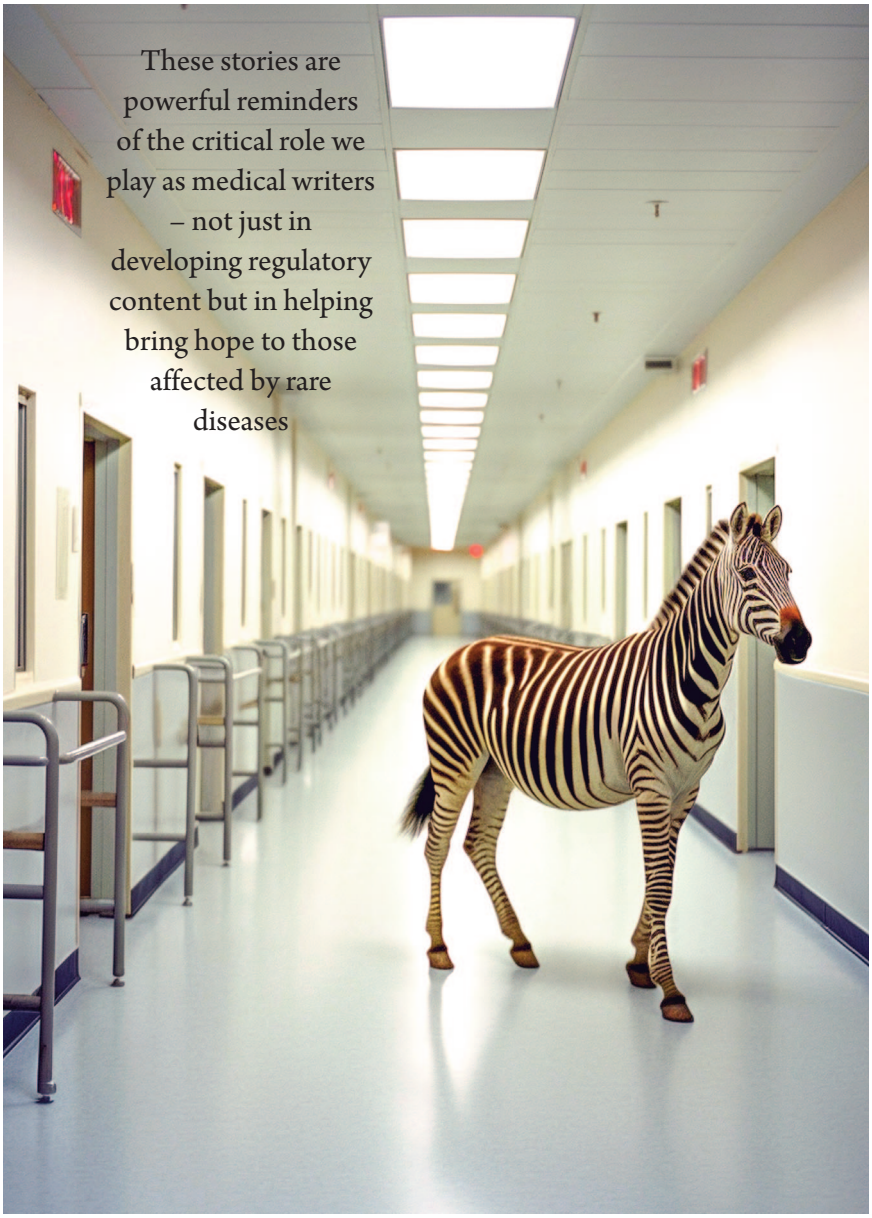
doi: 10.56012/fblb6643

"When you hear hoofbeats, think horses – not zebras."

Dear EMWA Colleagues,

This familiar adage is often taught to medical students to encourage simple, common-sense diagnoses. The idea is that the most straightforward explanation is usually correct. However, while it's a useful rule of thumb, it also risks overlooking the reality that "zebras" – rare diseases – do indeed exist.

In our increasingly globalised and interconnected world, it's easy to assume that modern medicine has all the answers. Imagine, for example, the awe of ancient Romans when Julius Caesar introduced the giraffe to Europe in 46 BC, with many believing it to be a cross between a camel and a leopard. Today's rare diseases – though certainly better understood than the giraffe was to the Romans – still present significant diagnostic and treatment challenges for medical professionals trained to expect the "horses" of common conditions.



I've seen this play out personally. For many years, my father-in-law was prescribed various treatments for persistent eczema, without relief. Only after an off-hand remark from a friend prompted him to get tested for coeliac disease did the pieces fall into place. His diagnosis led to the lifestyle changes that finally improved his condition.

On a professional level, I've also had the privilege of working on regulatory documents for novel products for the treatment of rare diseases. Reading patient testimonials about lives transformed by access to new therapies provided a sense of purpose and deep motivation. These stories are powerful reminders of the critical role we play as medical writers – not just in developing regulatory content but in helping bring hope to those affected by rare diseases.

In this issue of *Medical Writing*, we honour the zebras. Kelley Hill shares a career's worth of insights on regulatory writing for rare diseases. Sarah Milner interviews Richard Farquhar, who offers a candid look at living with a rare condition. Cheryl Roberts tackles diversity in trials for rare diseases, while Philip Burridge and Julie Eastgate discuss how master protocols can expedite such clinical studies. Christian J. Hendriksz discusses the pivotal role medical writers can play in providing hope to rare disease patients. Together, these stories and insights remind us of the profound impact we can have in helping turn the extraordinary into the possible.

Enjoy this issue and thank you for joining us in highlighting the vital work being done for those who live with rare diseases.

EMWA NEEDS YOU

EMWA is a member-run organisation

When you volunteer to assist EMWA in any capacity, you are furthering the development of our association.

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TO FIND OUT MORE

If you are a member of EMWA and eager to support ongoing initiatives, please contact info@emwa.org.

EMWA News

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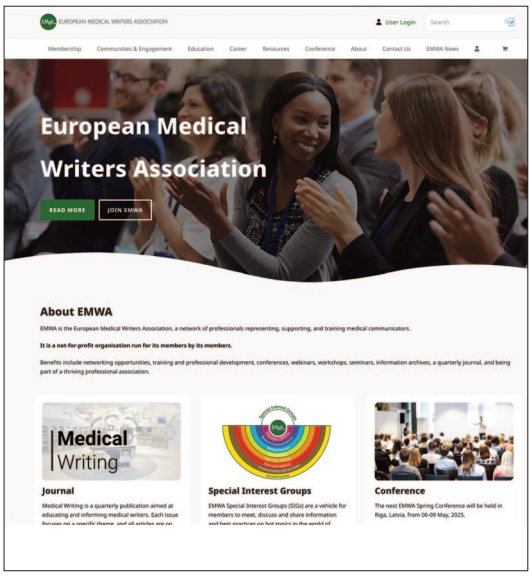
doi: 10.56012/vfnc6390

New EMWA website announcement

As you know, the new EMWA head office is now looking after us and we are in good hands.

During the transition process there were some unforeseen challenges, but we are on top of them. We are pleased to announce that the new website (EMWA.org) is live – there is some fine-tuning still to be done and this is being worked on in the background.



EMWA Special Interest Groups

EMWA membership allows you to participate in any **Special Interest Group** (SIG) Meet and Share, even if you are not an active member of that SIG.

These events are announced in the EMWA newsletter and in a separate mailing closer to the event date. The Meet-and-Share sessions are great opportunities to learn more about a particular topic in an informal setting. Some sessions may be recorded, but many are not.

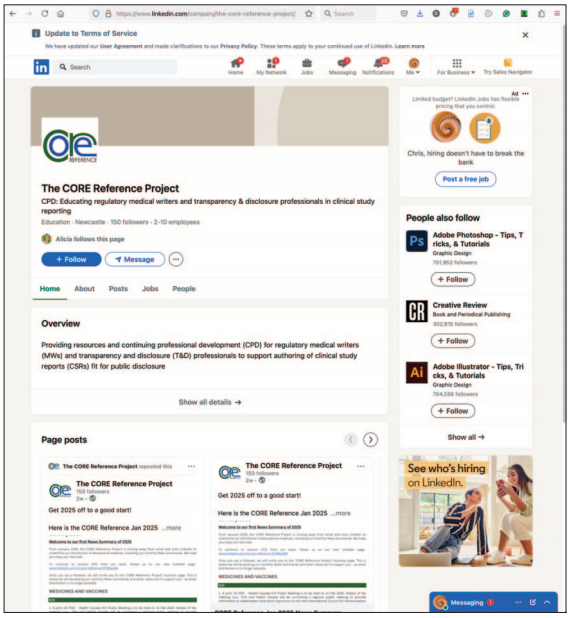
SIG members, on the other hand, participate in all SIG meetings (as their availability permits) and/or are more involved in the SIG activities, requiring an active role in providing more in-depth knowledge about what is going on in the SIG area.

If you are interested to know more about the SIGs, please read this: https://emwa.org/communities-engagement/find-communities/special-interest-groups-working-groups/

Did you know?

Existing EMWA members can receive a 10% discount off their next year's subscription for referring a new member to EMWA. For more information, please contact Head Office at info@emwa.org

Check out the back issues of EMWA's journal *Medical Writing* at https://journal.emwa.org!



CORE Reference

Get the December 2024 CORE Reference News Summary here: https://emwa.org/news/core-reference-news-summary-december-2024/

Technical issues are preventing us from reaching our "opt-in" community, so our usual bi-monthly emails will not go direct to your inbox.

The CORE Reference Project is moving away from email and onto LinkedIn to streamline our distribution of educational materials, including the monthly News Summaries: https://www.linkedin.com/company/the-core-reference-project/

Ambassador Programme news

The EMWA Ambassador Programme is continuing its efforts to reach out to new audiences to promote medical writing and EMWA and has supported the following events:

On Nov. 7, 2024, **Abe Shevack** and **Peter Llewellyn** spoke about the Ambassador Programme and Networking at the Opening Session of the 58th EMWA Conference. Abe fielded a number of questions afterwards about the programme and how volunteers can help support future activities.

On Nov. 15, 2024, **Maria Kołtowska-Häggström** and **Catherine Heddle** represented EMWA at Aula Medica in the Careers in Health and Science Exposition (ChaSE) conference in Stockholm, Sweden.

On Nov. 23, 2024, **Johanna Chester** presented Careers in Medical Writing and the benefits of joining EMWA at the University of Siena in Italy to the students of the Masters Programme in Scientific Biomedical Communication.

If you are an experienced medical writer and EMWA volunteer and are interested in becoming an EMWA Ambassador, or if you know of any upcoming career events in your locality, please contact the EMWA Head Office (info@emwa.org) or Abe Shevack (aspscientist@gmail.com).

webinar

EMWA Professional Development Committee webinar

EMWA webinars help members to develop skills and keep up to date with new or rapidly developing areas. Most of our webinars are live, online seminars with the opportunity for participant interaction. Webinar access is reserved for EMWA members only and requires registration.

For the planned or past webinars, please refer to this page: https://emwa.org/education/emwa-webinars-programme/

Living with a rare disease: A personal perspective

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Working in rare diseases especially, it is so important to just sit back and listen to the individuals who live with rare disease every day. As part of this edition of *Medical Writing*, guest editor Sarah Milner sat down with Richard Farquhar, who has a rare metabolic condition, phenylketonuria (PKU). He spoke about his life and his experiences and offered up some motivational works.

***Medical Writing* (MW):** So, Richard, can you just tell us a little about yourself?
Richard Farquhar (RF): Hi, it's lovely to speak to you. I'm currently in my early 40s, have a career in the higher education system in the UK, and I have 2 children who do not have the PKU condition.

I've been fortunate enough to have lived in the UK for my whole life, which has meant I've had access to PKU treatment and medical professionals. Over the past 5 years, I've taken a very focused approach to my PKU condition and overall health, fitness, and general well-being.

MW: For those who don't know, could you explain briefly what PKU is?
RF: PKU is a genetic condition, so it's something I've had to deal with my whole life. It's an inherited metabolic disorder in which an amino acid called phenylalanine (which is a building block of protein) builds up in the body and causes quite serious issues. When I eat foods with protein in them, which is pretty much nearly all food, phenylalanine enters the body. A person without PKU will be able to discard excess phenylalanine, but I cannot. Once phenylalanine increases to harmful levels it crosses the blood-

brain barrier and causes developmental issues and impacts the brain. Someone who is not treated will suffer intellectual disabilities and other serious health problems. There are different variants of the condition from mild to severe. Treatment is a lifelong, low-protein diet.

MW: Are there any medications you use to treat the disease?
RF: About a year ago, I started taking a drug called Sapropterin, which lowers the levels of phenylalanine in my blood. Since being on Sapropterin, I can tolerate 30 grams of protein from food daily. This still means I cannot eat meat, lentils, nuts, eggs, cheese, pastries, to name a few. Before Sapropterin I couldn't eat normal rice, or pastas. My tolerance for those foods is now quite good. But many PKU patients have very low tolerances, so I would guesstimate 80% of foods are not allowed on their PKU diet. The reliance then on medical-based food products is very high, and choice is very limited.

MW: Looking back, have you ever discussed with your parents how they felt when they found out their baby had PKU?
RF: My parents were very young when they had me, which I believe made it harder for them. I was also born in the early '80s, which was a very different time and still early in the treatment of the condition. They have told me they were terrified and fearful of the future. There were a lot of unknowns for them. They had to rely heavily on the medical professionals who were supporting people with the condition.

MW: As a follow-on, knowing what you know now, what advice would you give to someone who has just had a family member diagnosed with a rare disease?
RF: Firstly, don't panic. Time has moved on and medical science and knowledge about many condition has progressed. Also, there are a lot of people with my condition living amazing and full lives. It is a challenge, I will not lie, but I've lived a life full of family, friends, holidays, adventures, and fun. It's scary, but seek out up-to-date information, network with people with the condition to learn more, and access tailored care, if available to you. For me and my parents, the medical professionals I've had in my life have quite literally been a lifesaver.

MW: How do you feel having a rare disease has impacted your life (physically, mentally, socially)?
RF: There have been times in my life when it did impact it in a negative way. Food plays such an important part in how humans' bond; we socialise, and food plays an important part in that bonding process. How many times, when you've been with friends, is food part of the activity or process? How many times have you gone on holiday and wanted to experience the culture through food? I've had to find ways to adapt to so many situations, I've got better at that with practice and age, but in the early days, I missed out on some opportunities. Food science has progressed a long way in recent years, so this helps a lot. The biggest issues physically are that if I'm not tracking my food consumption well enough, and my phenylalanine levels are higher than they should be, I will experience headaches, brain fog, and a cognitive decline. It also impacts my overall mood and how I engage with the wider world. I'm at my best when I'm in control of my diet; controlling my phenylalanine levels is, for me, the foundation of everything.

MW: You are clearly a big advocate of exercise; do you feel like this helps you manage your condition physically or mentally?
RF: Yes. I think it has been one of the best decisions I've ever made. When a lot of people think of exercise, we just think it helps us get fitter and maybe stronger, but the effects go much deeper than that, and I'm living proof of this. Through focusing on exercise, I've become more mindful of my nutrition, my PKU condition, and my overall health and wellbeing. Exercise literally rewires our brain, for the better. It has a positive effect on our endorphins, which can cross the blood-brain barrier and make us feel better and happier. It's hard at the start to be motivated and to be consistent, but once you are, the positive effects are incredible. If medical science could take those positive effects and put all of them into a pill, not only would it have no side effects, but it would also be the best-selling pill ever created, forever. I've become psychically stronger and mentally stronger, it's impacted my life so much and is now starting to affect the lives of people around me (friends and family), and that's an amazing thing to see.

If medical science could take those positive effects of exercise and put all of them into a pill, not only would it have no side effects, but it would also be the best-selling pill ever created, forever.

MW: As your condition is essentially "invisible" to the outside world, I am interested to understand what, how, and when you tell people. Do you think that there is a stigma attached?
RF: When I was younger, I was not great at telling people, I would either avoid it or downplay it. I think that approach was not helpful. I'm quite open and honest about it now, with practice I've become better at explaining it too. I'm not ashamed of the condition, I have it, yes, but it's not who I am. I am much more than the disease. I will normally tell people when and if they ask, which can normally be around situations with food, which is all the time. Telling people is much easier now, there are a lot of food allergies that people throughout the world are faced with, though this is not a food allergy, it's much more severe than that, and it does make having the conversation easier.

MW: If this isn't too personal, did having a rare disease come into consideration when deciding to have children?
RF: Honestly, no. I knew that if my wife was not a carrier my children would not be born with the condition. Plus, it is a rare condition, so I treat it as such. I will not lie though, when both of my children were born, I was full of anxiety, especially when the heel prick blood test was taken. This is how they check newborn babies for the condition (and other conditions too). It was a very nerve-wracking time.

MW: I hear a lot that having a rare disease can be isolating. There is a lot of hate for social media, but I wonder if you see the positives of connecting with others in the community? Do you think it is useful for younger people too, I imagine in your teens, having a rare disease can be incredibly challenging socially.
RF: It can be very isolating yes. I spent 40 years of my life never meeting anyone face to face who had my condition. I messaged with a few people for years prior to that, thankfully because of social media platforms, but never met anyone until I went to my first PKU event in Birmingham, England. I've come to learn I get great strength from engaging with others with the condition, we can help, support, and understand each other, in a way that others can't. There is something very

healing about that. Social media gets a lot of bad attention, and rightly so, but I use social media to access the PKU community. I use it in ways to empower, to motivate me, I'm incredibly thankful for it and for the PKU community that engages with me. I think for everyone, no matter what their age, if they use it correctly, they can find people with the condition and they can potentially become lifelong friends. Having that type of support is amazing.

MW: Are there organisations that have helped you over the years and provided support and advice?
RF: Yes, the National Society for Phenylketonuria (UK NSPKU) is incredible. I didn't access the organisation for most of my adult life, and that was a mistake. The people who help run the organisation are amazing individuals, I have so much respect for them. The help and guidance they've given me and other people with PKU is incredible. I'm also thankful for medical professionals and organisations that create products, support research, and share information so that living with this condition can be a bit easier.

MW: OK, pivoting to a different topic and experiences with the healthcare system. Tell me more about the good and challenging experiences you have had with your care, and do you think this has changed over the years?
RF: Without access to the National Health Service (the UK's public health provider), I would not be the person I am today. I would not be living the life I'm living, and for that, I will be forever grateful. I know my parents are incredibly grateful for the support they had in those early years too. That doesn't mean everything is perfect though, there are always ways we can improve. The care across our country is equal in many ways, but not in many ways too. I'm aware there is a huge cost to treating this condition, for any healthcare provider, but the consequences of not, in my view, are much larger. I hope that across the world care for PKU becomes equal, it is needed. Also, there needs to be a more tailored approach to treating the PKU condition, and I hope to see more of this in the future. I have an amazing team of professionals around me now, and I am so thankful for having them in my life. There needs to be more access to products and the correct amount of supplements given to people who live with the condition, if these decisions are just made based on financial costs, the treatment will never be optimal, or even acceptable.

MW: Charities like Medics 4 Rare Disease do such important work educating medical students and doctors, but their work is limited by resources. There must be recognition of the patient/caregivers as the experts in their condition. Have you experienced this frustration where healthcare professionals (HCPs) don't listen to you?
RF: In the past yes. I've become very articulate and understand my body very well. I'm able to explain how and what I feel, but there have been times when this has not been listened too, or even interpreted as anxiety. Sometimes decisions made were purely financial, and I don't think that is putting the patient first. We live with the condition 24 hours a day, every day, and we have done for our whole life. In the past 5 years I've learned more about myself, the condition than I ever have. I'm proud of the learning I've gone through and how disciplined I've been, I've changed my life for the better, but there have been moments in the past where access to knowledge was limited, access to protein supplements were denied, and resources not good enough. I'm aware that medical staff have very limited time and resources themselves, and the pressures that they face to meet the requirements of all their patients very difficult. I'm thankful for all the treatments that I've had throughout my life, but treatment could be better for so many individuals, in the UK, and across the world. Thankfully, as I've said before, I have an amazing team of professionals around me now, and I'm so incredibly grateful for that.

> There is something very healing about that. Social media gets a lot of bad attention, and rightly so, but I use social media to access the PKU community.

MW: If you could offer up advice to healthcare professionals when working with a patient with a rare disease, what would that be?
RF: Try to ask the right questions and take the time to listen to their response. Be honest about any resource limitations you might have when dealing with any issues they are experiencing but show empathy too. The best advice I would give, is maybe try living on the [PKU] diet for one week yourself. It might be considered an unreasonable request, but it can be difficult to know the struggles of an individual until you've somewhat experienced what they are going through.

MW: Recently, I have seen a real move in pharma to develop treatments for patients with rare disease, which is so positive for the community. A lot of that is due to the regulatory agencies being more flexible around requirements for approval. Do you find it frustrating that, on the face of it, there isn't equal access for patients, and companies don't do work in rare disease because it won't make them lots of money?
RF: Yes, I think about this a lot. There are so many treatments coming through now that will make a clear difference in the lives of many, but finances play the biggest part in people getting access to them, and that's such a shame. There is a new drug called Palynziq which has the ability to help PKU patients progress onto a completely normal life, but there are some potentially risky side effects and the costs are huge. So far, I believe this is only being used in some states in the US due to cost. A lot of focus has been on the short-term implications of not treating rare disease conditions, but there are long-term implications of living on a diet that relies so heavily on processed food, I'm not sure that is being considered enough. Science is proving that this has long-term impacts for individuals, this needs to be considered more too. Approving these should be considered a priority.

MW: I also think that the regulatory agencies are really encouraging pharma companies to design trials that assess how a drug improves quality of life rather than just a finite endpoint like survival, etc. Do you see that as positive?
RF: Yes, in my view this is a huge positive step forward. Rare diseases effect every part of our lives, so assessing how quality of life is improved is just as important. A lot of managing the PKU condition focusses around phenylalanine levels, but it should be much more than just that.

MW: There is also a real move, especially in regulatory writing, to use more inclusive language in our documents I think the industry must move on from seeing clinical study participants as "subjects to observe". I know people generally go on trials to improve their health, but I was blown away but the people who go on clinical trials just to help generate

information on their condition. I think that's amazing.

Tell me about patient advocacy, why it is so important generally, and to you and why you share your journey on social media. What is your aim?

RF: I have a few aims and goals, firstly, it gives me a platform to connect with others, to share and learn new knowledge focusing on living with a rare disease. Also, there is limited research on rare diseases, exercise, and overall health, well-being, mental health and ageing with this condition, I hope that by sharing my journey in this area it will inspire people to share their voice and story and encourage new ideas and research in these topics. I hope to bring more awareness to the challenges we are faced with as a community, but to also be a positive role model for others.

MW: Looking to the future, what do you hope for in the rare disease community?

RF: Equal care and access to life changing treatments, across the world.

MW: Tell me what you want people to know about having a rare disease and how we can help your mission?

RF: I think helping patients have platforms like this is useful, so thank you for the opportunity, more opportunities like this would be helpful too. I want people to know that living with this condition is challenging for so many. It can either make or break you. So many people in general, who live a life without dietary constraints like the PKU diet struggle to follow a normal health or weight-loss diet plan for any period. It's why the fitness industry and the weight-loss industry are so big. People struggle, fail, then try again. People with my condition do not have this option, we must do this for life. It's more than that though, this is people's lives that are affected, their overall health, including their brain health harmed. Equal access to treatment that can change this would be amazing, and is needed. Think about that for a moment. Think of the strength it takes to be on a diet that for some, eradicates 80% of food options, forever. If this doesn't highlight that long-term treatment options need to be considered, and equal access to them, I don't know what does.

MW: Thank you so much for joining me today, Richard, and sharing your story. I really hope that in the future, there's a lot more research within this area.

Disclaimers

The views and opinions expressed in this article are the interviewers' and interviewees' own and are not necessarily shared by any employer or by EMWA.

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International PKU Day

International PKU Day is on June 28, a day on which we spread the word about Phenylketonuria (PKU). It also celebrates the legacy of Dr Robert Guthrie (1916-1995), and Dr Horst Bickel (1918-2000), who developed screening and treatment for PKU.

June 28 is also the deadline for the European Society for Phenylketonuria (ES-PKU) Sheila Jones Award, dedicated to patient advocates and organisations working for people with PKU.

Nominations for the award can be submitted at: https://www.espku.org/sheila-jones-award/sheila-jones-award-submission/.

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Essential investments in optimising clinical research for rare diseases

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doi: 10.56012/rqli4755

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Abstract

The complexities associated with clinical trials for (ultra) rare diseases include regulatory and logistical hurdles and the challenge of building trusting relationships with health authorities, patients, and clinicians. Significant obstacles include the identification of relevant endpoints, sample size limitations, and the cost of maintaining diverse clinical sites. Recruitment and retention of study participants are complicated by site inexperience and the specialised nature of rare disease management, necessitating comprehensive training of site staff and effective communication strategies. All these hurdles directly or indirectly impact the regulatory medical writer preparing complex rare disease clinical documents that comply with regulatory and industry standards.

Introduction

The definition of *rare disease* varies between countries or territories, being a disease or condition affecting fewer than 200,000 patients in the US or with a prevalence of ≤5 per 10,000 inhabitants in the EU.[1] *Ultra-rare* diseases are defined as rare diseases that have a prevalence of <1 per 50,000 persons.[2,3] The field of clinical research for rare diseases presents distinct challenges that significantly influence study design, execution, and outcomes.[4–7] The limited research available for rare conditions complicates the identification of relevant literature and the development of robust clinical protocols. Furthermore, developing positive relationships with patients and clinicians is a vital part of executing a rare disease clinical trial. Here, we discuss the complexities of conducting clinical trials for (ultra) rare diseases, with particular focus on regulatory and logistical hurdles, and on the importance of building collaborative and trusting relationships. The success of such trials requires significant upfront investment of time (and money) building solid foundations with regulatory authorities, patient groups, key opinion leaders, and clinical sites, to shape an executable protocol. Regulatory medical writers play a key role in preparing this protocol and other complex rare disease clinical documents that comply with regulatory and industry standards. In an area where experience is limited, every participating person or organisation is a trailblazer in their field and any process or system is deployed in an unfamiliar manner.

Protocol and study design

Given the complexities of rare diseases, where conventional research frameworks may not be directly applicable, it is crucial to invest adequate time upfront to develop a well-designed, executable protocol in collaboration with experts. This will ultimately save time, cost, and frustration. Rushing the process increases the regulatory medical writer's burden because of the need for multiple protocol amendments, which likely result in delayed study timelines as well as increased costs.

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Critical factors that must be addressed when designing trials for rare diseases include:

- **Primary and secondary endpoints:** Identifying appropriate primary and secondary endpoints is complex because of limited existing data. The rarity of the disease may require novel or adapted endpoints (including patient reported outcomes) to accurately assess treatment efficacy and safety. In the absence of relevant endpoints, surrogate endpoints or biomarkers may be considered when agreed by the health authority. Involving a rare disease patient advocacy group (when available) may prove valuable in determining relevant and nuanced endpoints[8] as rigid interpretation of predetermined endpoints may result in an unfair *study failure* of an effective treatment.
- **Sample size and data points:** Achieving an adequate sample size is challenging because of the scarcity of eligible participants. A careful balance should be considered between sampling frequency and the burden on the patient and study personnel. A small sample size can undermine the statistical power of the study, complicating the determination of significant outcomes,[9] while intensive sample collections for sufficient data points may discourage both patients and investigators. Statistical methodology is critical to handle missing data, patients lost to follow-up, and interpretation of outcomes with small sample size.
- **Control arm and dosing:** Determining an appropriate control arm and dosing regimen is another difficult area. Given the rarity of the condition, standard control groups[10] may be unavailable, and dosing strategies must be tailored based on limited pre-existing data.

The US Orphan Drug Act of 1983 and similar legislation in the EU encourage companies to develop drugs for rare diseases. Drugs are granted an orphan designation if they are for the treatment of rare diseases that are life-threatening or seriously debilitating.[1] Securing orphan designation for a drug can provide advantages such as access to protocol assistance from regulatory authorities.[11,12] Unlike common conditions, rare diseases often require numerous and iterative communication with health authorities, thus falling under this assistance procedure. The lack of established precedents can increase the likelihood of disagreements and delays, as both the applicant and the regulatory body must navigate uncharted territory. Therefore, investing early in relationships with health authorities and incorporating their input on protocol design and endpoint agreements, along with contributions from patient advocacy groups, key opinion leaders, and clinical sites, will lead to improved study design.

> Traditional clinical trial management systems are not optimised for rare disease studies, and key performance indicators are not applicable because of the low participant numbers.

Inclusion and funding of clinical sites

Collaborating with clinical sites at the time of protocol development will help ensure that the protocol is executable and reduce the need for protocol amendments at a later stage. However, while inclusion of clinical sites at an early stage is of great benefit, for rare disease trials this is complex and far more costly than for standard trials. Qualification criteria for clinical sites to run rare disease trials are unclear or complex, patient pathways may be unknown, and networks for referrals may not be set up. Prevalence or incidence data regarding a condition are very limited and often reflect regional epidemiological data only; this complicates assessing which countries should be in scope for the trial. Clinical trial naïve sites often need to be included for rare disease studies, adding to the complexity both in defining the site selection criteria as well as in the conduct and execution of the trial. However, given the low probability of identifying eligible participants, qualification of a sufficient number of sites is crucial. Funding considerations include supporting single sites across multiple countries rather than consolidating sites within one or two countries and maintaining these international study sites even when participant recruitment is minimal. In addition, the international regulatory approval system is complex; this may cause lengthy delays for clinical trial set-up.[13] Sites recruiting no or only a few patients annually require high maintenance and bespoke communication, as risk-based monitoring is insufficient because of low enrolment numbers. Traditional clinical trial management systems are not optimised for rare disease studies, and key performance indicators are not applicable because of the low participant numbers. In addition, the often-inexperienced site personnel must undergo extensive training (further discussed below) and attend investigator meetings for potentially enrolling only one participant, if any.

> Given the small number of eligible participants, all sites that are willing to recruit are indispensable and investment in optimising coordination, communication, and the relationship with the site in general is crucial.

Recruitment and site support

Screening, recruiting, enrolling, and retaining participants in rare disease clinical trials present unique challenges. Practical aspects of recruitment and retention in clinical trials of rare diseases were previously discussed by DeWard et al.[14] Here, we add our experiences to the authors' collective experience.

Naïve sites

Clinical sites selected for (ultra) rare disease trials may be inexperienced with running clinical trials in general or with rare disease trials specifically. Therefore, the investment in education of clinical site personnel, regarding clinical trial processes, systems, and disease awareness for potential referral sites, should not be underestimated. The site may not have a study coordinator if there was never a need for such a role before, and contracting may be outsourced given that hospitals are often very large organisations. The local investigator might be unaware of how to conduct internal follow-ups and likely has a full-time role without a structured framework for clinical trials. Therefore, any email, phone call, or request from the sponsor could feel like an additional burden while many of the activities required for trial success may need to be highlighted on a regular basis. Coordination by a single point of contact at the sponsor to a specifically appointed coordinator at the clinical site may help the investigator navigate both new worlds: of clinical trials and of the rare condition. This involves clarifying acronyms for roles and

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processes that may be unfamiliar to site personnel and ensuring that the site comprehends the study processes both within their own organisation and in relation to the sponsor. Personnel may have been trained months or even a year before their first patient is enrolled; continued site engagement and support during the period between start-up and first participant enrolment may avoid the need for re-training. Once a patient has been identified, it is important to ensure that site support is available throughout the entire clinical trial journey for that patient. Establishing relationships based on trust and collaboration with open communication between the study sites and sponsor may help to prevent issues such as: following standard care protocols where these are not appropriate, missing timepoints in irregular study follow-up schedules, and reporting normal ranges of laboratory values where these are not applicable. In short, lack of experience can result in deviations from required study processes and inappropriate reporting. Therefore, it is essential to slow down and explain things gradually and comprehensively, without presuming any prior experience from the clinical staff or their organisation. This can help ensure the site is set up for success when they do identify a suitable participant. Furthermore, facilitating connections between participating sites is critical for trial success, for enquiries or support, and to aid information sharing and lessons learnt related to best practices, challenges and successes.

The integrity of rare and valuable study samples (further discussed below) may be at considerable risk at inexperienced sites. No experience with specific analyses requires shipping from a clinical site to the laboratory where the applicable assays are available. No experience with sample handling may result in shipping delays resulting in sample loss or samples that cannot be analysed. Training of local site personnel may be considered for sample analysis; however, this may not always be possible because of the specific infrastructure, facilities, and expertise required for sample handling and analysis. Local analysis at multiple sites may also result in unwanted inter-assay variation, which will have a considerable impact on the results, considering the small sample size. Investment for the highest anticipated benefit should be considered: use an established central laboratory, involving shipping risks and possibly high maintenance costs, or use local laboratory analyses, which may be more costly and result in inter-assay variation.

It is essential to slow down and explain things gradually and comprehensively, without presuming any prior experience from the clinical staff or their organisation.

Expert sites

Sites with specialised knowledge may face challenges if overwhelmed by multiple requests. It is key to understand the position of the site to ensure interactions do not become a burden or irritation. Here too, established coordination through a dedicated point of contact at the sponsor to a specifically appointed coordinator at the clinical site can facilitate task prioritisation, reduce the burden on the local investigator, and prevent frustration. This sponsor contact may also share expert learnings with the other participating sites. Given the small number of eligible participants, all sites that are willing to recruit are indispensable and investment in optimising coordination, communication, and the relationship with the site in general is crucial.

Eligible participants and study burden

Another challenge to screening and enrolling eligible patients is the correct diagnosis of the rare condition. A condition may be so hard to identify that patients often have consulted several different specialists over many years before they are accurately diagnosed. In contrast, recruitment of pregnant individuals whose foetus has a rare condition is only feasible within a limited time frame during the early phase of the pregnancy.

Minimising blood sampling in very young children while maximising data collection from the limited number of participants should be considered to minimise participant study burden. Numerous exploratory endpoints may increase any participant burden because of increased blood sampling, more or longer visits, or additional questionnaires. Other study-related requirements may also be perceived as a burden, such as the number or type of treatments or injections, or having to alter medication that patients are already taking. There is a need to carefully consider what is important to prevent the protocol from being overburdensome. Participants may drop out of a study if the burden is perceived as too high, thereby reducing the already minimal analysis set. Given the (ultra) rare condition, it will likely prove impossible to recruit additional eligible participants. This underlines the value of each single obtained study sample, and therefore the importance of positive participant experiences for optimal retention. Swift stipend timing should not be underestimated as part of this positive experience. Effective communication between the participant's primary care

team and the study team is also essential to ensure their care team is provided with the study information and understands what the participant has already been through.

Considerations for the regulatory medical writer

All hurdles discussed above directly or indirectly impact the regulatory medical writer. As best practices may not be available or will evolve during the trial, study design decisions or strategy positions or both may not be clear or confirmed prior to the start of writing protocols, protocol amendments, or health authority communications. Both the lack of background information on the (ultra) rare disease and the lack of rare disease guidance with TransCelerate[15] template(s) can be a challenge with all clinical document types. The regulatory medical writer will likely encounter many more rounds of review and revisions than usual, because of continuously advancing insights regarding best practices for the specific rare condition. Close collaboration with the study team is essential, anticipating continuous study and document adjustments and preparing for health authority interactions at all stages of the study and document submission.

The regulatory medical writer will likely encounter many more rounds of review and revisions than usual, because of continuously advancing insights regarding best practices for the specific rare condition.

Protocol amendments

The pioneering nature of rare disease trials often leads to frequent protocol amendments, both before and during the trial. Common areas for adjustment include:

- **Inclusion and exclusion criteria:** With improved diagnostic methods, laboratory assessments or disease management guidelines, modifications may be necessary to better align with the actual patient population.
- **Study design and recruitment:** Changes to study design or participant numbers may be needed if initial recruitment targets are unmet. A redesign may accommodate the available participant pool or real-world data may be considered, complementing the prospectively collected clinical data, for meeting the required sample size and acceptable statistical interpretation.
- **Study sites:** New sites may be added, or existing sites closed, throughout the trial's duration.

Study reports

Writing the clinical study report for rare diseases can be challenging because of exceptions such as study procedure deviations, incomplete data sets, and adjusted analysis methods. Incomplete data sets due to participant dropout or discontinuation of investigational treatment may be a significant part of the analysis. Descriptive decision rules may be employed to draw conclusions from available data when statistical significance is difficult to achieve. Lean report writing and maintaining anonymity are difficult as clinical teams are more inclined to provide in-text narrative descriptions for each individual participant because of the small sample size. This feature of a rare disease clinical study is not covered in reporting guidelines, making it difficult to reach cross-functional agreement on a common reporting approach. Note that for both the patient narratives and for the lay summary, maintaining anonymity is exceptionally important, given the small number of trial participants.

Conclusion

Conducting clinical trials in rare diseases demands a nuanced approach that addresses the unique challenges of limited research, regulatory interactions, inexperienced clinical sites, and participant recruitment. Ensuring adequate time is allowed upfront to develop a solid foundation will enhance the likelihood of a well-designed, executable protocol. For rare disease trials, both the pace and way of working need to be adjusted. By understanding these dynamics, investment in positive relationships with authorities, clinicians and patients, and preparing for potential protocol amendments, researchers can better navigate the complexities of rare disease trials. Strategic planning and flexibility are key to regulatory document development and advancing treatments to improve outcomes for patients with rare conditions.

Acknowledgements

The authors would like to thank Karen Badwal, Judy Crane, Bethany Drury, Danny Hasselbaink, and Wande Osuntokun for their valuable input, content review, and editorial assistance.

Disclaimers

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

Disclosures and conflicts of interest

All authors are employed by Johnson & Johnson Innovative Medicine. The authors declare no conflicts of interest.

References

1. Franco P. Orphan drugs: the regulatory environment. Drug Discov Today. 2013;18(3-4):163–72. doi:10.1016/j.drudis.2012.08.009
2. Hughes DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? QJM. 2005;98(11):829–36. doi:10.1093/qjmed/hci128
3. Harari S. Why we should care about ultra-rare disease. Eur Respir Rev. 2016;25(140):101–3. doi:10.1183/16000617.0017-2016
4. Day S, Jonker AH, Lau LPL, et al. Recommendations for the design of small population clinical trials. Orphanet J Rare Dis. 2018;13(1):195. doi:10.1183/16000617.0017-2016
5. Pizzamiglio C, Vernon HJ, Hanna MG, et al. Designing clinical trials for rare diseases: unique challenges and opportunities. Nat Rev Methods Primers. 2022;10;2(1): s43586-022-00100-2. doi:10.1038/s43586-022-00100-2.
6. Milner S, Kusmierczyk AR, Taccoen J. The unique challenges of clinical trials in rare disease: a regulatory writer's perspective. Med Writ. 2023;32(1):54–7. doi:10.56012/cwaa8066
7. Mishra S, Venkatesh MP. Rare disease clinical trials in the European Union: navigating regulatory and clinical challenges. Orphanet J Rare Dis. 2024;19(1):285. doi:10.1186/s13023-024-03146-5
8. Gaasterland CM, Jansen-van der Weide MC, Vroom E, et al. The POWER-tool: recommendations for involving patient

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representatives in choosing relevant outcome measures during rare disease clinical trial design. Health Policy. 2018;122(12):1287–94. doi:10.1016/j.healthpol.2018.09.011

9. EMA. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical trials in small populations. London: 2007 Feb 1. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf.
10. EMA. ICH Topic E 10 Choice of control group in clinical trials. Step 5: Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). London: Jan 2001. Available from: https://www.ema.europa.eu/en/ich-e10-choice-control-group-clinical-trials-scientific-guideline
11. EMA. Orphan designation: overview [cited 2024 Nov 05]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview
12. FDA. Special protocol assessment guidance for industry. Apr 2018 [cited 2024 Nov 13]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/special-protocol-assessment-guidance-industry
13. Crow RA, Hart KA, McDermott MP, et al. A checklist for clinical trials in rare disease: obstacles and anticipatory actions – lessons learned from the FOR-DMD trial. Trials. 2018;19(1):291. doi:10.1186/s13063-018-2645-0
14. DeWard SJ, Wilson A, Bausell H, et al. Practical aspects of recruitment and retention in clinical trials of rare genetic diseases: the phenylketonuria (PKU) experience. J Genet Couns. 2014;23(1):20–8. doi:10.1007/s10897-013-9642-y
15. TransCelerate. Clinical Content & Reuse solutions [cited 2024 Nov 05]. Available from: https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions.

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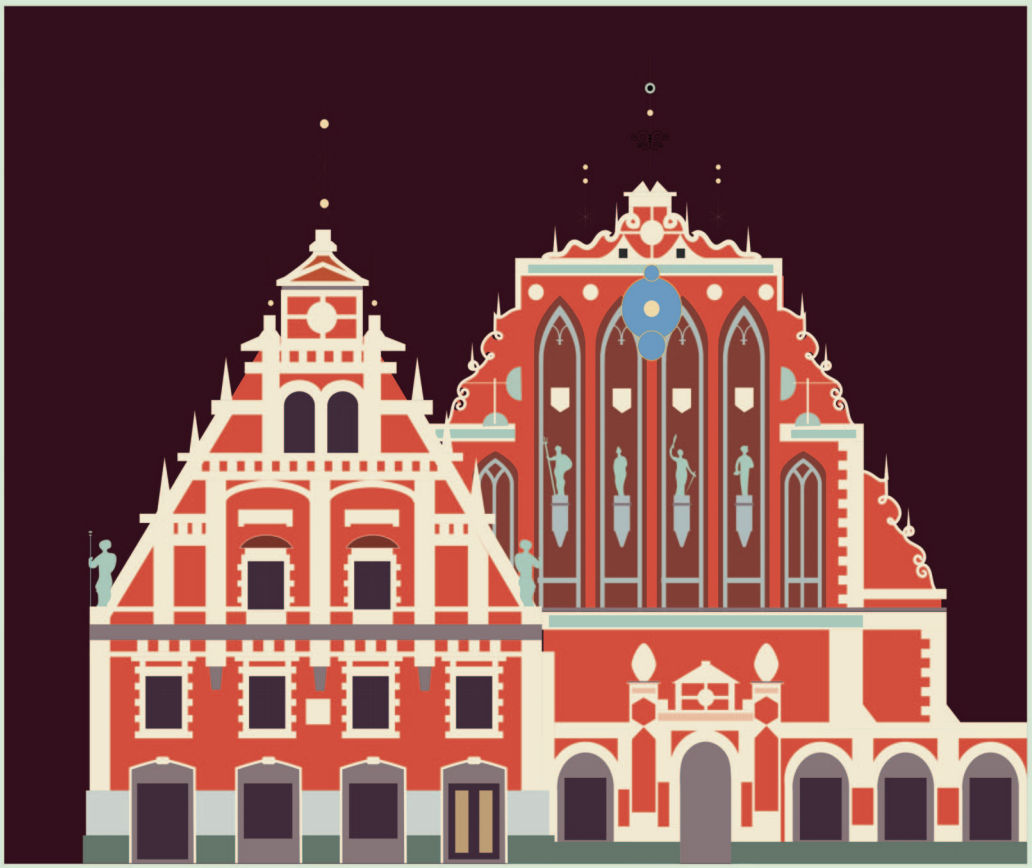

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Regulatory writing for rare disease: An interview with Kelley Hill

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Abstract

Over her 40-year career, Kelley Hill has become regarded as an industry expert in strategic, high-quality, and impactful regulatory writing, especially in the rare disease space. Now enjoying a slower pace of life having retired in 2023, she has led highly successful writing departments in pharma, including at Shire, Certara, and, most recently, Alexion, and contract research organisations (CROs). *Medical Writing* guest editor Sarah Milner asked her about her experience as a writer in rare disease over the years.

***Medical Writing* (MW):** So, Kelley, maybe you could introduce yourself and talk a little bit about your career over the years in this field?

Kelley Hill (KH): For me, like many other writers, medical writing was not my first career, but it became the best job of my life! All my prior work and education experiences across academia, pharmacology, research, drug development, and management contributed to my start as an editor in a wonderful medical writing group. With time, mentoring, and peer support, I expanded my skill set and developed clinical regulatory, clinical trial transparency, and scientific writing experience across complex therapeutic areas. It was diverse! My experience spanned work at big pharma, small pharma, and rare disease companies, and included a few great years in a contract writing organisation. The rare disease space is where I am most fulfilled, though! I have had terrific opportunities to build, lead, and collaborate on medical writing and cross-functional teams supporting regulatory submissions. The most important aspect, though, was working in partnership with other medical writers, and knowing we had talents and skills that together made great teams.

MW: What is it about working in rare disease that you enjoy?

KH: There are many reasons that make working in the rare disease space rewarding! I have been fortunate to be able to meet with patients and their families, and to hear how difficult their journeys are (they average 7 years before diagnosis). It is enormously rewarding to know that the medical writer's work on key regulatory documents can help clear the approval pathway for drugs to treat their diseases and hopefully improve their and their families' quality of life.

> The review of the submission varies between the FDA and EMA.

In my experience, medical writers who work in the rare disease space are extra inquisitive and need to be terrific communicators. It is not uncommon to have a medical lead who comes from academia and is somewhat unfamiliar with regulatory documents. I love working with these writers who really work hard to develop pleasant and efficient rapport with teams, all while maintaining calm professionalism and respect for all.

In addition, the research and science supporting drug development for rare diseases is fascinating. It requires innovative approaches to identifying the biology that underlies the condition. It also requires thoughtful, intelligent approaches to identify clinical endpoints that accurately reflect the effect of the investigational agent on the disease markers. This science drives everything from the bench to the intended patient population. Amazing.

And finally, it is my honour to be able to collaborate with some of the brightest minds in research, medicine, regulatory, statistics, safety, medical writing, and clinical operations to develop a well-planned and cogent portfolio of documents – documents that support regulatory evaluation and, hopefully, approval.

MW: Are there any areas you find frustrating about working in rare disease?

KH: Well, as EVERY medical writer knows, it is a challenge when key reviewers do not, or are not, able to provide their input in early stages of document development. Major revisions at the supposed "last draft" causes a lot of anxiety, because the timelines generally are not designed to accommodate extra work time.

Also, because rare diseases have little or no clinical or regulatory precedent, I try to anticipate potential impact of late changes when the full data is finally in a format that allows reviewers to make sure their hypotheses fit with the intended label language.

One area that is a challenge is seeing how information is extrapolated and interpreted for the public. Patient summaries, a required element of transparency and disclosure, need time and extensive discussions in order to accurately describe complex clinical endpoints and disease mechanism of action in plain language.

MW: Do you see key differences between writing for rare diseases for the FDA and EMA? If so, could you expand on those?

KH: The European Union (EU) nations have nationalised healthcare that varies by country with regard to reimbursement. It can be challenging to try to ensure that the benefit:risk ratio is clear and inclusive of the intended population with an eye to the country where the population is located.

Another big difference is the regulatory requirements for disclosure of clinical information. The implementations of Policy 0070 and the Clinical Trial Information System (CTIS) in the EU are extremely challenging in the rare disease space. Anonymising individual data can still pose a risk of disclosing that patient's personal data (PPD), given the limited number of patients with the disease. In addition, protecting commercially confidential information (CCI) also presents a challenge, as disclosure of unique processes used to develop and manufacture drugs for rare diseases can provide competitors with valuable insight and information.

In addition, the review of the submission varies between the FDA and EMA. The FDA evaluation begins in Common Technical Document (CTD) Module 5 with the raw data, and works up the CTD ladder with the Clinical Overview as its penultimate summary. The EMA begins its evaluation with the Clinical Overview, then moves to additional details in the Summaries (M2.7.x), finishing with the data in Module 5. So it is important for both organisations that the entire suite of documents present consistent and accurate representations of every measure, and provide clear summaries that focus on those measures.

MW: Writing about rare diseases, in the context of things like paediatric investigation plans (PIP), orphan drug designations (ODD), even summary modules, is hard and emphasises the need for a writer to write concisely and strategically for the agencies. What challenges have you experienced with writing documents in this area and how can we negate them?

KH: Success comes with planning, and any time there were challenges, it was because there was insufficient thought and strategy dedicated to the project or projects before the writing began. Often, teams want to jump in and start documents before there is a fully fleshed-out strategy. One frequent deficiency is a lack of a robust risk assessment to balance out the potential outcome intended. For example, if the disease only occurs in children aged 2 and older, the PIP must include a clear rationale for excluding children under age 2.

Over-writing, also known as waxing rhapsodic, is a common pitfall when the strategy is not complete or clear. It is a real challenge to gain a team's trust to be allowed, as a writer, to transform a wordy document into one that is concise, non-repetitive, and clear.

Negating the challenges is, I believe, a collaborative effort with many cross-functional stakeholders in order to ensure smart, efficient document development.

MW: One of the greatest challenges can be actually finding the data, things like prevalence/incidence. What sources can help with this?

KH: In my experience, my colleagues in epidemiology have been fantastic resources. They have access to literature, databases, metadata reviews, etc., and have skill sets suited for what can be a real investigational challenge.

If that resource is not available, then the writer can search the literature for early research on the disease or family of diseases. Experts in the field may also be able to provide insight, and colleagues in medical affairs have proved to be invaluable in connecting with those individuals for their knowledge.

Kelley Hill

MW: Clinical trial diversity is a hot topic, this includes for rare disease, which can be really challenging! Maybe you could give us some tips on what to consider when authoring generally and, specifically, for a rare disease indication?

KH: While I am not anywhere near an expert on this topic, I have worked with colleagues in patient advocacy and other groups who keep a close eye on ensuring inclusivity and identifying challenges for the subjects to be included in rare disease clinical trials. Here is where the prevalence or incidence information can be key, although representation in some areas of the world is incomplete at best. Input from other global sites, health organisations, and patient groups should help flesh out a best effort.

Authoring a diversity action plan is a new arena! It requires input from many sources and will require informed regulatory and legal leadership to ensure compliance.

MW: Kelley, we would like to thank you for your time. It is so appreciated, and we hope you enjoy your retirement!

Disclaimer

The views and opinions expressed in this article are the interviewees' own and are not necessarily shared by any former employer or by EMWA.

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Writing for orphan drugs:
A compass to navigate document types and regional requirements

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doi: 10.56012/suws8001

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Abstract
Medical writing for rare diseases encompasses the development of various regulatory documents that are required to obtain orphan drug designation and marketing authorisation for treatments targeting rare conditions. Effective planning and close collaboration with key stakeholders are essential to navigate regional regulatory requirements and address unmet patient needs, ultimately facilitating the approval of treatments for rare diseases.

Introduction
Rare diseases are serious, chronic, progressive diseases that affect a small number of individuals. The definition of a rare disease based on its prevalence is not universal and varies across jurisdictions. In Europe, a disease is considered to be rare when it affects fewer than 5 per 10,000 people.[1] It is estimated that about 36 million people live with a rare disease in Europe,[1] which represents approximately 5% of the European population.

The first compilation of diseases with low prevalence dates back to 1581, with the publication of *Medicinalium observationum exempla rara, recognita et aucta* by Rembert Dodoens.[2] Five hundred years later, the advances in scientific

knowledge have led to the identification of between 6,000 and 8,000 rare diseases, with new diseases regularly described in medical literature. Approximately 80% of rare diseases have a genetic cause, 70% have a paediatric onset, and about 95% lack approved treatments.[3,4] Because of the lack of approved treatments, the off-label use of prescribed drugs is common among patients with these conditions.

Several interrelated factors contribute to the deficit of treatments for rare diseases:

- **High development costs** with limited potential for return on investment due to small market size.
- **Long development timelines** due to the prolonged trial recruitment periods in small populations.
- **Lack of or poor understanding** of the pathophysiological mechanisms and the natural history of these diseases.
- **Difficulty in generating confirmatory evidence** using traditional trial designs due to the small and usually heterogeneous patient population. In this scenario, innovative designs and novel endpoints are required for obtaining substantial evidence of efficacy and safety.
- **Limited collaboration and data sharing** through registries and collaborative networks and databases hinder the collection of robust data to inform and optimise clinical trial design.

Regulatory agencies play a crucial role in supporting the development of drugs for rare diseases through various mechanisms and programmes designed to address the unique challenges associated with these conditions. One of these mechanisms is the orphan drug status that incentivises the development of treatments for rare diseases by providing benefits such as scientific advice and market exclusivity. The EMA offers several programmes to expedite drug development and approval, including conditional marketing authorisation, marketing authorisation under exceptional circumstances, or the PRIority MEdicines (PRIME) scheme. Similarly, the US FDA provides programmes such as Fast Track, Priority Review, Breakthrough Therapy Designation, and Accelerated Approval.

Regulatory agencies play a crucial role in supporting the development of drugs for rare diseases through various mechanisms and programmes designed to address the unique challenges associated with these conditions.

Overview of orphan drug status

The process for applying for orphan drug status varies between regions and countries. An overview of application procedures and content is provided for the EU, US, and Japan (refer to Table 1); other jurisdictions with orphan drug legislation include Singapore, Australia, South Korea, and Taiwan.[5] Some regions and countries collaborate when evaluating orphan drug applications; for example, EMA encourages simultaneous applications to the US and Japan.[6] Presubmission meetings may be requested before applying for orphan drug status, in which case the medical writer is likely to be involved in the preparation of one or more briefing packages as well as the orphan drug application.

In the EU, an application for orphan drug designation (ODD) is made by submitting a form via the EMA Regulatory & Scientific Information Management Platform (IRIS). The scientific part of the

Table 1. Summary of orphan drug status in selected regions/countries

Country/ region (agency)	Prevalence criterion	Scientific advice	Financial incentives	Other incentives
EU (EMA)[13]	< 5 in 10,000 people affected in the EU	Yes[a] – Protocol Scientific Advice	• Reduced fees for protocol assistance and regulatory activities	• Potential access to conditional approval • Market exclusivity after approval (10 years; 12 years for medicines that also have complied with an agreed PIP)
US (FDA)[14]	< 200,000 people affected in the US	Yes[a]	• Exemption from scientific advice fees • Tax credits for qualified clinical trials • Grant funding for research[b]	• Potential market exclusivity after approval (7 years)
Japan (NIBIO, MHLW, PMDA)[15]	< 50,000 people affected in Japan	Yes, including PMDA priority consultation system	• Reduced fees for PMDA priority consultation system • Subsidies for development costs; tax credits for trial expenses	• Priority review • Extension of re-examination period (10 years for drugs; 7 years for devices)

Abbreviations: EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; MHLW, Ministry of Health, Labour and Welfare; NIBIO, National Institute of Biomedical Innovation; PIP, paediatric investigation plan; PMDA, Pharmaceuticals and Medical Devices Agency; US: United States.

[a] Recommended parallel submission with US FDA and EU EMA.

[b] Orphan drug status is not required for grant funding but is encouraged.

Table 2. Sections of the EMA Orphan Drug Designation Application Form[6,7]

Section	Overall topic	Details of content
A	Description of the condition	A1. Details of the condition (definition, aetiology, specific characteristics, classification, diagnosis, and symptoms) A2. Proposed orphan indication. A3. Medical plausibility (active substance, description of the medicinal product and information on the plausibility of the orphan condition including supportive data). A4. Justification of the life-threatening or debilitating nature of the condition
B	Prevalence of the condition	B1. Prevalence of the orphan disease or condition in the EU B2. Prevalence and incidence of the condition in the EU
C	Potential for return on investment	C1. Grants and tax incentives C2. Past and future costs C3. Production and marketing costs C4. Expected revenues C5. Certification by registered accountant
D	Other methods for diagnosis, prevention or treatment of the condition	D1. Details of any existing diagnosis, prevention, or treatment methods D2. Justification as to why methods are not satisfactory D3. Justification of significant benefit
E	Description of the stage of development	E1. Summary of the development of the product E2. Details of current regulatory status and marketing history in the EU and non-EU countries

Abbreviations: EMA, European Medicines Agency; EU, European Union.

Note: ■ shaded sections are those for which the medical writer is most likely to act as the author; ■ non-shaded sections are those for which the medical writer collaborates with other functions.

form, which is the most likely to require medical writing input, consists of five sections designated A to E as shown in Table 2, plus a bibliography (Section F). Per EMA guidance, Sections A to E should generally be a maximum of 30 pages.[7] For Sections A, D, and E, the latest Investigator's Brochure and any recent briefing packages are likely to provide useful information as a starting point. Key collaborators for these sections include clinical science, regulatory affairs, and biostatistics. Section B is likely to require specialist epidemiology input. Section C is typically only required if the usual prevalence requirement of less than 5 people per 10,000 in the EU is not met and the application is instead being made based on insufficient return to justify the necessary investment.

In the US, the requirements of an orphan drug application are set out in Title 21 of the US Code of Federal Regulations (CFR) Section 316.20(b), as summarised in Table 3. The length is expected to be approximately 20 to 30 pages, similar to the EMA application, and medical writers are likely to work on similar content. The application can be submitted using Form FDA 4035. Use of this form is optional as long as the equivalent information is included; however, the form contains useful guidance on the quantity of text and type of information required. Further guidance is available in an FDA webinar.[8]

In Japan, orphan designation is based on Article 77-2 of the Pharmaceutical Affairs Law and applications are made via the Ministry of Health, Labour, and Welfare. The application can be submitted using the Application Form for Orphan Drug/Medical Device Designation Consultation; as with the US, use of the form is optional but recommended. Note that the form is in Japanese and the application must be submitted in the local language; a copy of the form annotated in English is also available.[9] A summary of the required content is provided in Table 4.

Considerations for writing orphan drup applications

As shown in Tables 2, 3, and 4, there is substantial overlap among jurisdictions in terms of orphan drug application content. It can therefore be efficient to create a single core document containing information that can be repurposed for individual applications, such as details of the drug, the disease background, justification for why the drug is needed, and supporting data. The latest Investigator's Brochure and any recent briefing packages are likely to provide useful content as a starting point.

Prevalence data need to be researched and written separately for each application as it is specific to each region/country; specialist epidemiology input is recommended.

Content on why existing treatments are insufficient may also need to be adapted for different jurisdictions, as each market may have a different range of authorised treatments. The approval dates for widely authorised treatments are also likely to differ. It can be useful to include

Table 3. Overview of required content for a US Orphan Drug Application[8,16]

Subsection of 21 CFR Section 316.20(b)	Overall topic	Details of content
1	Identity of the rare disease or condition	• Statement that the sponsor requests ODD for a rare disease or condition • Specific identify of the disease or condition
2	Administrative information	• Sponsor contact details • Generic and trade name of the drug if available, or the chemical name or a meaningful descriptive name of the drug • Name and address of the source of the drug if it is not manufactured by the sponsor
3	Disease background	• Description of the rare disease or condition for which the drug is being or will be investigated • Proposed use of the drug • Reasons why such therapy is needed
4	Description of the drug	• Active moiety (small molecules) or features of molecular structure (macromolecules) • Physical and chemical properties • Scientific rationale for the use of the drug for the rare disease or condition, including all relevant data
5	Clinical superiority (if applicable)	When is it applicable? If the drug is a "same drug" as an already approved drug[a] for the same rare disease or condition for which the sponsor is requesting an ODD. What must be included? An explanation of why the proposed variation may be clinically superior to the first drug.
6	Orphan subset (if applicable)	When is it applicable? If the ODD request is for a drug for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people. What must be included? A justification that, due to one or more properties of the drug, the remaining people with the disease or condition would not be appropriate candidates for use of the drug.
7	Regulatory status/ marketing history	A summary of the regulatory status and marketing history of the drug in the US and other countries. Any adverse regulatory actions taken against the drug in any country.
8	Population estimate	Documentation, with appended authoritative references, to demonstrate that: (i) Fewer than 200,000 people in the US have the disease or condition, or would otherwise receive the drug per year if it is a vaccine or diagnostic OR (ii) If 200,000 or more people in the US are affected by the disease or condition, or would otherwise receive the drug per year, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the US

Abbreviations: CFR, Code of Federal Regulations; ODD, orphan-drug designation; US, United States.

[a] The concept of "same drug" is defined in 21 CFR 316.3(b)(14)

appendices in the core document detailing the significant benefits over each existing treatment; content from the relevant appendices can then be included in each application.

The timing of each orphan drug application may need to be carefully considered in the context of the marketing application timing, as some countries/regions may require the marketing application to be filed within a certain period of time after the ODD is approved.

Documents for orphan drugs at the time of applying for approval

Medical writers should be prepared to support additional orphan-drug-related documents in the lead up to submission of an EMA marketing authorisation application.

During the review of a marketing authorisation, the EMA assesses whether a drug continues to meet the criteria for maintaining its orphan status. An orphan maintenance assessment report must be submitted to provide relevant information; exact timing of the submission depends on whether the review is

Table 4. Overview of required content for an orphan drug application in Japan[9]

Overall topic	Details of content
Product details	• Name of active substance • Composition of investigational product • Outline of manufacturing process • Expected dosage and route of administration
Expected indication	• Justification of significant benefit in Japan • Description of the target disease (summary of the cause and symptoms, prevalence of the condition, and justification as to why existing methods are not satisfactory) • Medical plausibility, including the mechanism of action and clinical data • Summary of current regulatory or development status, and marketing history outside Japan • Summary of current development status and plan of the product in Japan
Administrative information	• Details of the sponsor and contact details for the application • Submission date

accelerated. The report should include information on the current prevalence of the condition or the potential return on investment (as applicable based on the original ODD application), the current life-threatening or debilitating nature of the condition, the current existence of other methods for the diagnosis, prevention or treatment of the condition, and, if applicable, a justification of the drug's significant benefit. A template is available from the EMA website.[10] The orphan maintenance assessment report is subject to public disclosure, as it is included in the European Public Assessment Report (EPAR).

If EMA has already granted marketing authorisation and a period of market exclusivity for an orphan "similar medicinal product", an orphan similarity report must also be submitted.[10] A similar medicinal product is defined in Article 3 of Commission Regulation (EC) No 847/2000 as "a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication". The assessment of similarity is based on the principal molecular structural features of the product, the mechanism of action, and the indication. Even if a drug is assessed as being a similar medicinal product, marketing authorisation may also be granted for the same therapeutic indication under certain circumstances, including in cases where the second medicinal product can be shown to be safer, more effective, or otherwise clinically superior. In this case, a critical report justifying clinical superiority to the authorised product must be submitted. There are parallels with the "same drug" considerations for a US orphan drug application (see Subsection 3 in Table 3), although any information already used for that purpose may need to be updated and adapted for the EU rather than the US.

Close collaboration with clinical science and regulatory affairs is necessary to ensure that the core messaging is up to date and in line with the rare disease/orphan drug possibilities offered in the applicable jurisdiction.

Additional peri-approval documents for orphan drugs

Before applying for marketing authorisation, a briefing package may be developed to specify which type of application or regulatory pathway the sponsor believes is the most appropriate, considering the epidemiology of the disease in the region of interest, the existing treatments, and the pathways available in the region.

The rationale for selecting a particular type of application or regulatory pathway may also be required as part of the responses to the questions received during the assessment of a marketing application by the agency. The selected regulatory strategies may also evolve over time as new data from clinical trials become available. Close collaboration with clinical science and regulatory affairs is necessary to ensure that the core messaging is up to date and in line with the rare disease/orphan drug possibilities offered in the applicable jurisdiction.

After authorisation

Approval of orphan drugs may be granted with limited data on safety and efficacy via routes such as accelerated marketing approval (FDA), or conditional marketing authorisation or approval under exceptional circumstances (EMA). After authorisation, however, regulatory agencies may require the marketing authorisation holder to conduct additional postmarketing studies and clinical trials that provide confirmatory information on the efficacy, safety, pharmacokinetics/pharmacodynamics or use in special populations.

Marketing authorisation holders are required to report the status of these studies annually. While FDA uses Form FDA 3989[11] to facilitate the submission and ensure consistency of annual status reports, EMA requires a clinical overview addendum (COA) among other documentation.[12] Medical writers often drive development of the COA, the clinical summaries, and the reports that summarise the results from the studies conducted to accomplish the agency requirements. Similarly to other regulatory documents, collaboration and early planning are essential to effectively develop these documents. Medical writers should work closely with other functions from document conception to ensure that the statistical outputs and the associated messages enable a critical evaluation of the status of fulfilment of the agency requirements. Furthermore, thorough planning allows the re-

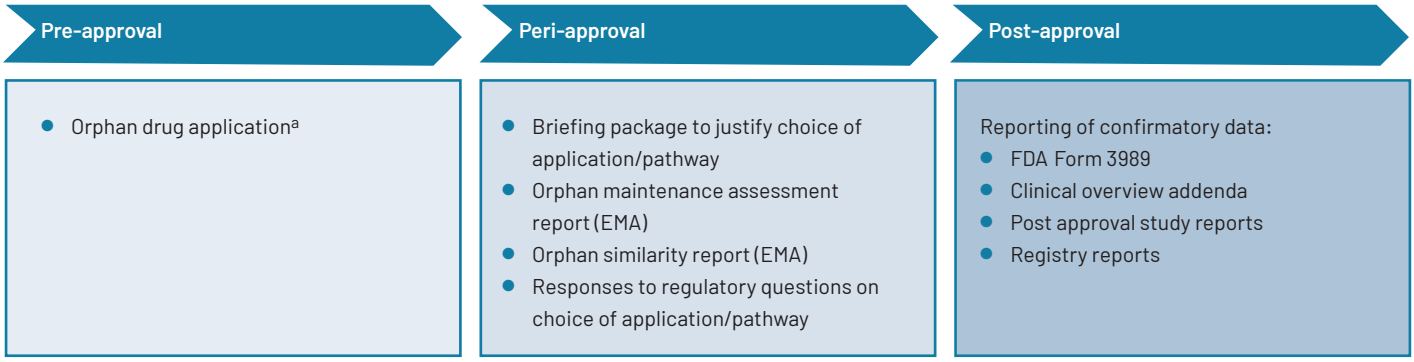

Figure 1. Overview of documents in orphan drug development

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.

[a] In the United Kingdom, orphan drug designation can only be requested at the time of marketing application.

purposing and reuse of content among documents.

Summary

Medical writing for a rare disease indication for which orphan drug status is sought requires several additional document types to those required in traditional drug development pathways. Regional variations in process and requirements can pose challenges; however, careful planning, judicious reuse of material, and close collaboration with other functions ensures success and ultimately addresses unmet needs in patients, which is extremely rewarding.

Acknowledgements

The authors would like to thank Sarah Frost of PPD Clinical Development Services at Thermo Fisher Scientific for reviewing a draft of this manuscript.

Disclaimers

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

Disclosures and conflicts of interest

The authors declare no conflicts of interest.

References

1. European Commission. Public Health. Rare Diseases and European Reference Networks. Rare Diseases [cited 2024 Nov 25]. Available from: https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/rare-diseases_en
2. Dooms MM. Rare diseases and orphan drugs: 500 years ago. Orphanet J Rare Dis. 2015;10:161. doi:10.1186/s13023-015-0353-3.
3. Orphanet Report Series. Medicinal products for rare diseases in Europe. 2024. [cited 2024 Nov 25]. Available from: https://www.orpha.net/pdfs/orphacom/cahiers/docs/GB/Medicinal_products_for_rare_diseases_in_Europe.pdf
4. Global Genes. Allies in Rare Disease. Rare disease facts. 2024 [cited 2024 Nov 27]. Available from: https://globalgenes.org/rare-disease-facts/
5. Chan AY, Chan VK, Olsson S, et al. Access and unmet needs of orphan drugs in 194 countries and 6 areas: a global policy review with content analysis. Value Health. 2020;23(12):1580–91. doi:10.1016/j.jval.2020.06.020.
6. EMA. Applying for orphan designation. 2024 [cited 2024 Nov 25]. Available from: https://www.ema.europa.eu/en/human-

regulatory-overview/research-development/orphan-designation-research-development/applying-orphan-designation
7. Official Journal of the European Union. Commission Notice. Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another 2022/C 440/02 (2022) [cited 2024 Nov 25]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52022XC1121(01)
8. US FDA. Designating an orphan product: Drugs and biological products. 2024 [cited 2024 Nov 25]. Available from: https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products
9. Ministry of Health, Labour, and Welfare of Japan. Brief instructions for the application form of orphan drug designation [cited 2024 Nov 25]. Available from: https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/20120618_02.pdf.
10. EMA. Applying for orphan designation: orphan designation. 2024 [cited 2024 Nov 25]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/orphan-designation-marketing-authorisation/applying-marketing-authorisation-orphan-medicines.
11. US FDA. Guidance document. Annual status report information and other submissions for postmarketing requirements and commitments: using forms FDA 3988 and FDA 3989 guidance for industry. 2023. [cited 2024 Nov 25]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/annual-status-report-information-and-other-submissions-postmarketing-requirements-and-commitments
12. EMA. Renewal and annual re-assessment of marketing authorisation. 2024 [cited 2024 Nov 25]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/renewal-annual-re-assessment-marketing-authorisation Sources:
13. EMA. Orphan incentives. 2024 [cited 2024 Nov 27]. Available from https://www.ema.europa.eu/en/human-regulatory-overview/research-development/orphan-designation-research-development/orphan-incentives
14. US FDA. Medicinal products for rare disease and conditions. 2024 [cited 2024 Nov 27]. Available from: https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions
15. Ministry of Health, Labour, and Welfare of Japan. Overview of orphan drug/medical devise designation system. 2024 [cited 2024 Nov 27]. Available from: https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html
16. US FDA. Orphan Drug Designation Request Form. 2024 [cited 2024 Nov 25]. Available from: https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-designation-request-form

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Guest Editors: Sampoorna Rappaz and Lisa Chamberlain James

Innovative use of master protocols for pivotal studies in rare diseases

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doi: 10.56012/lmmt8627

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Abstract

Recent years have seen the development of clinical study protocols that introduce more complex design features into the usual gold-standard randomised controlled trials (RCTs). Complex protocols are potentially useful for drug evaluation in the setting of rare disease indications, to optimise the efficiency of investigational drug development. They often involve a development of a master protocol alongside disease-specific sub-protocols. This article describes an approach used to develop a complex protocol for a Phase 3 trial involving an investigational treatment being studied for use in two distinct rare diseases. In a somewhat unusual approach, detailed subprotocols were developed that contained all information required by the investigator, while the master protocol highlighted differences between the subprotocols and provided rationale justifying use of a complex study design. Use of complex study designs aims to promote efficiency in the clinical investigation process but also needs to offer optimal clarity to both study investigators and regulatory reviewers.

Clinical trials in rare diseases

Rare diseases affect around 400 million people globally; however, 95% of these diseases lack an approved treatment.[1] According to an analysis of clinical trials in Europe, the USA, and Japan in 2018, most clinical trials into rare diseases consider rare cancers.[2] Costs and other challenges involved in undertaking such clinical trials are increasing, with evaluation of investigational treatments being particularly difficult when patient recruitment is limited by the small numbers of individuals affected. Other challenges that can limit clinical trials for rare diseases include: poor understanding of disease course and characteristics; difficulties in following regulatory guidance in the context of small patient numbers; issues with manufacturing and supply of investigational drugs; as well as safety and financial risks.[3] This means that undertaking randomised controlled trials (RCTs), the established gold standard for evidence of drug efficacy and safety, can be difficult in the rare-disease setting.

Agents intended to treat rare diseases are usually termed orphan drugs. A major factor that compromises the development of orphan drugs is the cost of the process and small market potential. These issues require the use of novel approaches to optimise treatment options for this underserved groups of patients.

This article describes our recent experience using a somewhat novel approach to complex protocol design that was used to assess a treatment in the rare-disease setting. In this case, the protocol was for a Phase 3 trial involving an investigational treatment being studied for use in two distinct rare diseases.

Use of novel master protocols to date

Recent years have seen the development of clinical study protocols that introduce more complex design features into the gold-standard of RCTs, to optimise the efficiency of investigational drug development.[4] There is potential for some of these complex-design approaches to help bring treatments to market for individuals with rare diseases.

The use of master protocol designs has led to great advances in cancer therapy. For example, this approach was used to investigate the activity of imatinib in treating 186 patients with 40 different malignancies ranging from solid tumours to haematologic cancers.[5] The study was conducted as a basket trial, in which a common treatment combination was investigated across multiple disease cohorts and outcomes were assessed in the context of relevant genetic mutations; multiple disease types were in effect collected together in a "basket".

Another approach uses an umbrella trial whereby multiple therapies are evaluated for a single disease. National Cancer Institute–Molecular Analysis for Therapy Choice (NCI-MATCH) was an umbrella trial that investigated whether treating cancers according to their molecular abnormalities was effective; NCI-MATCH enrolled an impressive 1,593 participants who were each assigned to one of 38 sub-protocols.[6]

> Matrix studies involve multiple clinical interventions and patient populations, and in effect can be considered a combination of a basket and an umbrella study.

Platform studies are designed to prospectively add or discontinue sub-studies. As such they have a fluid structure, which allows multiple targeted therapies to be studied in populations with similarities such as a common disease. An example of a platform study is the Systemic Therapy for Advancing or Metastatic Prostate Cancer (STAMPEDE) trial in men with newly diagnosed advanced prostate cancer. From its start in 2005, STAMPEDE included almost 12,000 participants; the trial is ongoing, but recruitment is now closed.[7] The first results demonstrated improved disease control and life expectancy by adding docetaxel or abiraterone to treatment regimens; however, since then the fluid structure of the study has allowed many other strategies to be tested.

Matrix studies involve multiple clinical interventions and patient populations, and in effect can be considered a combination of a basket and an umbrella study. In common with platform studies, matrix studies can remove interventions and include new interventions as the study progresses. Matrix studies need not have a fixed duration or sample size.

These various types of studies offer a range of design options that can be incorporated into large

Photo: freepik

and complex protocols. While cancer has been the clinical setting that has most frequently utilised novel study protocols, other areas of clinical research are also embracing this change.

A survey in 2021 found that master protocols had been used in infectious disease, neuroscience, immunology, and rare disease settings, with the most common design being basket trials.[8]

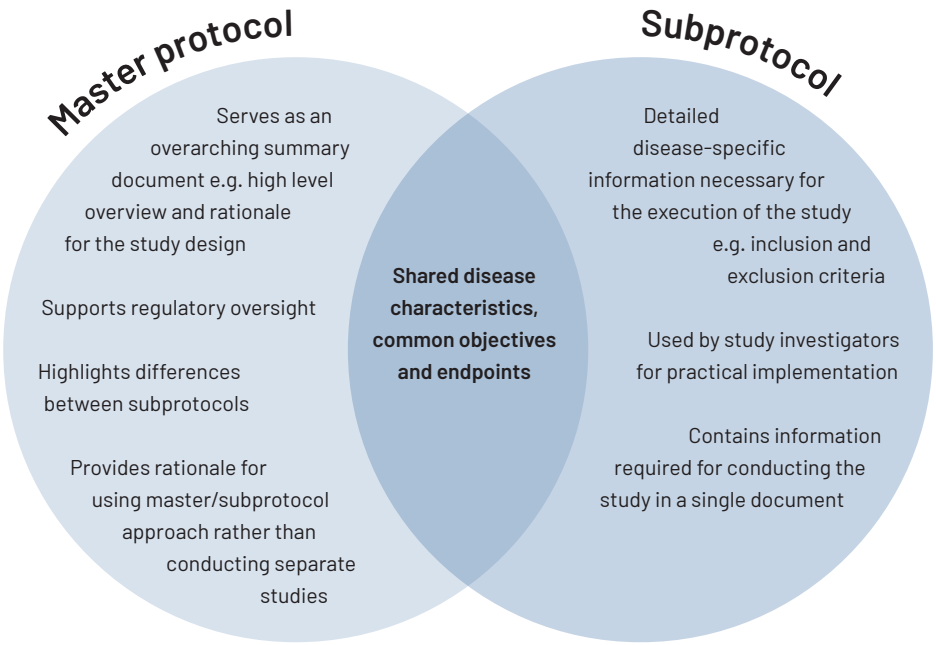

Figure 1. Venn diagram showing how the master protocol and sub protocols interacted within the complex protocol design

Available guidance on the use of master and sub protocols

Assistance in developing master protocols is available in the form of templates, such as those provided by EU Patient centric clinical trial platforms (EU-PEARL).[9] More detailed guidance is also available from sources such as the US FDA[10] and TransCelerate Biopharma.[11] However, how useful these templates are depends upon various factors, including the disease setting and experience and expectations of the study development team. Guidance documents generally describe the development of a master protocol that includes detailed description of clinical study design; the associated subprotocols then describe disease-specific aspects to highlight the differences between subprotocols.[9,10,12]

Experience in developing master and sub protocols in the rare-disease setting

A protocol was required for a pivotal Phase 3, double-blind, randomised, multicentre, placebo-controlled study, whereby two rare diseases were to be investigated with the same therapeutic agent. This led to developing master and sub protocols (Figure 1).

Our approach was to prepare detailed disease-specific sub protocols (rather than a detailed

Similarities	Differences
Share similar disease characteristics, faciltating the use of many common endpoints	Each subprotocol has its own control group, due to potential differences in disease progression profiles or rates between the conditions under study
Common database setup	Sample size calculation
Comparable visit/assessment schdules between subprotocols	Stratification variables
Use of single independent safety monitoring committee	Disease inclusion and exclusion criteria

Table 1. Summary of the similarities and differences between the disease-specific sub protocols.

master protocol) that included all the usual information expected in a protocol for an RCT; the master protocol then served as a summary document that presented an overview of the study, highlighted differences between the two subprotocols, and provided the rationale for use of the master/subprotocol approach rather than conducting separate studies. In this setting, the subprotocol becomes a document that is predominantly used by the investigator, with the master protocol supporting regulatory oversight.

Development of detailed subprotocols was considered to promote clarity for study investigators, as all information required for conducting the study was included in a single document (rather than having to consult a master protocol for common aspects and the subprotocol for disease-specific aspects). Use of the complex study approach was intended to rationalise operational aspects, allowing for a common database set-up, comparable visit/ assessment schedules between subprotocols, and use of a single independent safety monitoring committee. In addition, conducting a single study in multiple rare-disease populations can help with accrual of a more substantial body of safety data for the investigational treatment. In the rare-disease setting, these considerations can help overcome some of the challenges associated with drug development in very small patient populations.

Comparison of the two subprotocols highlighted differences that would be expected, primarily reflecting different disease inclusion and exclusion criteria, sample size calculation, and stratification variables (Table 1). In this particular study, numerous similarities in disease characteristics facilitated use of many common endpoints.

In addition, conducting a single study in multiple rare-disease populations can help with accrual of a more substantial body of safety data for the investigational treatment.

A major difference in approach, compared with many other complex-design studies, was that each subprotocol had its own control group. Use of a common control group across sub-studies is often used, to facilitate accrual of a larger body of data relating to the investigational agent and to ensure that as many participants as possible receive the potentially beneficial investigational treatment. In the context of rare diseases, it can be applicable to include individual control groups given the potential for the disease-progression profile or rate to differ between the conditions under study.

The protocol was submitted as part of a Clinical Trial Application by the Sponsor of the clinical study through the Clinical Trials Information System (CTIS) and subsequently approved. Regulators comments were as expected for a Phase 3 protocol with minor changes required. The structure of a master protocol and subprotocols was approved without resistance to the concept. The master and sub protocols will all be registered as one clinical study. The clinical study is due to start in 2025 and the protocol will be submitted to additional countries and regions globally.

Conclusions

Conducting clinical trials into new investigational agents to treat rare diseases that provide robust evidence of safety and efficacy can be difficult, expensive, and timely to perform. The use of a master protocol with disease-specific subprotocols has the potential to improve the efficiency of drug development for such indications. We describe experience developing a clinical trial with a master protocol/subprotocol design, whereby a single investigational drug was assessed in two rare diseases. The approach taken in developing the master/subprotocols aimed to promote efficiency of the clinical investigation process and offer optimal clarity in both process and design to both study investigators and regulatory reviewers.

Acknowledgements

The authors would like to thank Melanie Colegrave for her assistance in preparing this article.

Disclaimers

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

Disclosures and conflicts of interest

The authors declare no conflicts of interest.

References

1. Global Genes. Rare disease facts [cited 2024 Nov 14]. Available from: https://globalgenes.org/rare-disease-facts/
2. Sakate R, Fukagawa A, Takagaki Y, et al. Trends of clinical trials for drug development in rare diseases. Curr Clin Pharmacol. 2018;13(3):199–208. doi:10.2174/1574884713666180604081349
3. Milner S, Kusmierczyk AR, Taccoen J. The unique challenges of clinical trials in rare disease: a regulatory writer's perspective. Med Writ. 2023;32(1):54–7. doi:10.56012/cwaa8066
4. Mackinnon J, Gisbert A. Master protocol studies: embracing the "new normal". Med Writ. 2021;30(3):83–9. Available from: https://journal.emwa.org/media/4017/mew-303-final-published-issue.pdf
5. Heinrich MC, Joensuu H, Demetri GD, et al. Phase II, open-label study evaluating the activity of imatinib in treating life-

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threatening malignancies known to be associated with imatinib-sensitive tyrosine kinases. Clin Cancer Res. 2008;14(9):2717–25. doi:10.1158/1078-0432.CCR-07-4575

6. O'Dwyer PJ, Gray RJ, Flaherty KT, et al. The NCI-MATCH trial: lessons for precision oncology. Nat Med. 2023;29(6):1349–57. doi:10.1038/s41591-023-02379-4
7. STAMPEDE. 2024 [cited 2024 Nov 27]. Available from: https://www.stampedetrial.org/
8. Li X, Lu C, Broglio K, et al. Current usage and challenges of master protocols-based on survey results by ASA BIOP oncology methodology working group master protocol sub-team. Ann Transl Med. 2022;10(18):1036. doi:10.21037/atm-21-6139
9. EU-PEARL. EU-PEARL's Suite of master protocol templates. 2023 [cited 2024 Nov 14]. Available from: https://eu-pearl.eu/eu-pearls-suite-of-master-protocol-templates/
10. US FDA. Master protocols: efficient clinical trial design strategies to expedite development of oncology drugs and biologics guidance for industry. 2022 [cited 2024 Nov 14]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and
11. TransCelerate. Clinical content & reuse solutions. 2024 [cited 2024 Nov 27]. Available from: https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/
12. European Commission/European Medicines Agency/Heads of Medicines Agencies (EC/EMA/HMA). Complex clinical trials – Questions and answers. Version 2022-05-23. 2022 [cited 2024 Nov 27]. Available from: https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf.

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Model-informed drug development in rare diseases

An introduction for medical writers

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doi: 10.56012/sbrq7799

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Abstract

Model-informed drug development (MIDD) approaches maximise and connect information obtained on a drug during development, allowing better characterisation of its risk: benefit profile. MIDD is especially useful for rare diseases with few patients to study. Children represent more than half of patients affected by rare diseases, most of which are genetic. In recent years, submissions for rare diseases have come to rely on modelling and simulation, and regulators now expect their inclusion in dossiers. All types of regulatory documents are impacted by MIDD, from protocols to product labels. The ability to translate complicated scientific information into comprehensive text is particularly vital in MIDD due to its complex nomenclature and multifaceted data outputs.

Model-informed drug development (MIDD) is defined as the strategic use of computational modelling and simulation methods that integrate non-clinical and clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence to guide decision making during drug development and regulatory evaluation.[1] MIDD approaches provide a quantitative framework to maximise and connect all the information obtained on a drug during development, enabling extrapolation of that data to unstudied situations and populations.

By building models of drug concentrations and/or drug responses over a time course (pharmacokinetics [PK]), we can understand how the amount, frequency, and duration of dose affect drug concentration and demonstrate the relationship between the drug concentration and pharmacodynamic (PD) responses. These models also help to characterise the PK/PD variability of drugs and the clinically relevant factors contributing to variability. Ultimately, MIDD aims to expedite drug development, enhance regulatory science, and produce benefits for patients.[2] While MIDD can be applied to all therapeutic areas, rare diseases have a greater need for MIDD because of the smaller number of patients available for study.

> The requirement for experienced medical writers to support regulatory and medical communications in rare disease will grow in the future.

MIDD in drug development and assessment

MIDD is not new, with MIDD first contextualised by the International Council for Harmonisation (ICH) in Guideline E4.[3] In the 1990s, it was largely used experimentally to support drug development programmes, but was not pivotal to decision making. However, it is now at the cornerstone of 21st century pharmacological research,[4] with the use of "Population PK", "PK/PD" and "Exposure-Response" embedded in drug development and a critical part of many international regulatory guidance documents and frameworks.[5]

Global regulatory agencies, such as the EMA and the US FDA , recognise the value MIDD provides during drug development and assessment and have been collaborating with the ICH and focused working parties to develop a harmonised guidance to optimise its use. The new overarching ICH M15 "General Principles for Model-Informed Drug Development (MIDD)" has very recently been endorsed by the ICH assembly for public consultation.[1] This guideline aims to facilitate greater and wider adoption of MIDD principles in drug development and regulatory decision making across the major ICH regions (Europe, Japan, and the US), and among the standing worldwide regulatory and industry members, as well as ICH observers (e.g., the WHO).

During the past decade, the EMA has published papers on MIDD, drafted guidelines that discuss modelling and simulation approaches, created a working party, and hosted MIDD-centric workshops that promote the use of MIDD in dose-finding. The EMA has produced guidance documents on the use of MIDD approaches in: paediatric drug development, which has significant overlap with the rare disease space (approximately 50% to 70% of rare diseases affecting children[6] are genetic in nature); drug-drug interaction risk assessment; renal and hepatic impairment; obesity; and pharmacogenetics.

The FDA has incorporated MIDD into regulatory guidance and review processes, with the MIDD Paired Meeting Programme as part of the Prescription Drug User Fee Act (PDUFA) VII commitment. Designed to promote early interactions between drug developers and the FDA on the use of modelling approaches to support a drug's development, the MIDD Paired Meeting Programme will undoubtably further facilitate and increase the use of MIDD in rare disease research.[7]

In recent years and particularly since 2021, submissions for rare diseases have come to rely heavily on the modelling and simulation provided as part of MIDD. While it used to be a supplemental part of the dossier, regulators now expect the inclusion of modelling in the dossier.

The importance of MIDD in rare disease

High costs and long timelines due to limited patient populations and the lack of validated endpoints are associated with rare disease drug development, along with a multitude of other unique challenges for clinical trial design and completion. Rare diseases represent a significant unmet medical need. While 7,000 to 10,000 rare

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diseases affecting over 350 million people worldwide[8] have been identified and described, it is estimated that only around 5% of rare diseases have an FDA-approved drug.[9] The majority (~80%) of rare diseases are genetic,[10–12] with children representing more than half of all patients affected by rare diseases. Staggeringly, approximately 30% of children with these debilitating diseases will not live to their fifth birthday.[8] Traditionally, treatment strategies for genetic disorders were not generally aimed at targeting the underlying genetic mutation, but were designed to treat or manage the associated signs and symptoms of the disease. However, today, disease-modifying drugs, such as nucleic acid-based therapies, are now under development.

From a medical writing perspective, there has been a significant increase in publications pertaining to rare or orphan diseases in the last two decades – from less than 2,000 in 1996 to around 6,000 in 2012 to 2014.[13] Furthermore, in 2023, 28 of 55 (51%) of FDA novel drug approvals received orphan drug designation

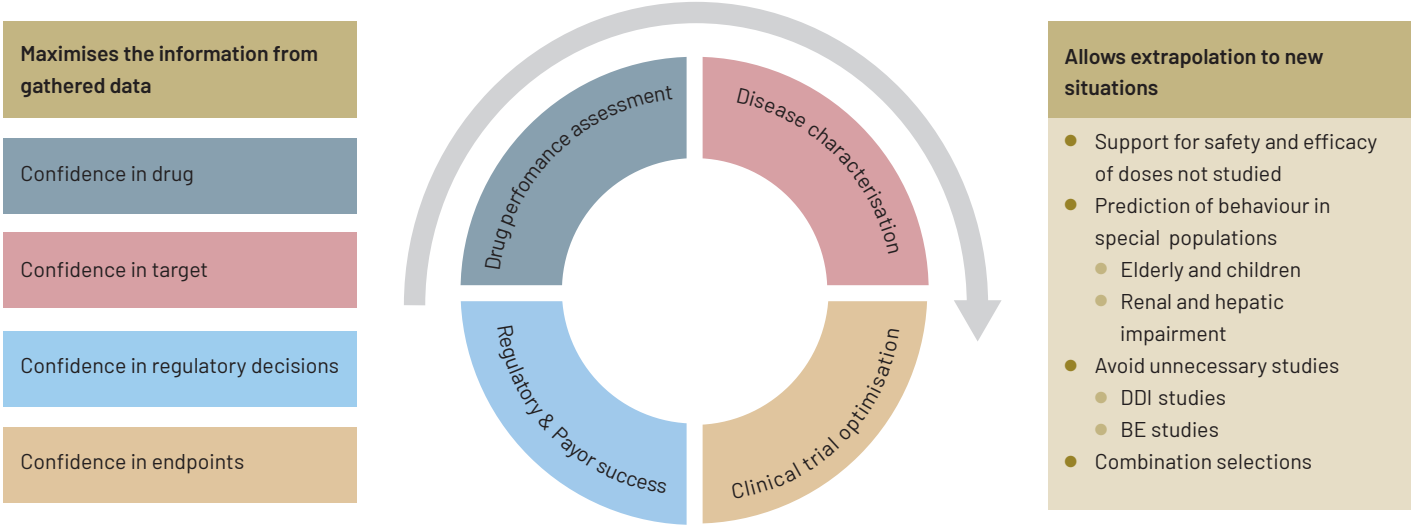

Figure 1. Why is MIDD so powerful?

Abbreviations: BE, bioequivalence; DDI, drug-drug interaction; MIDD, model-informed drug development.

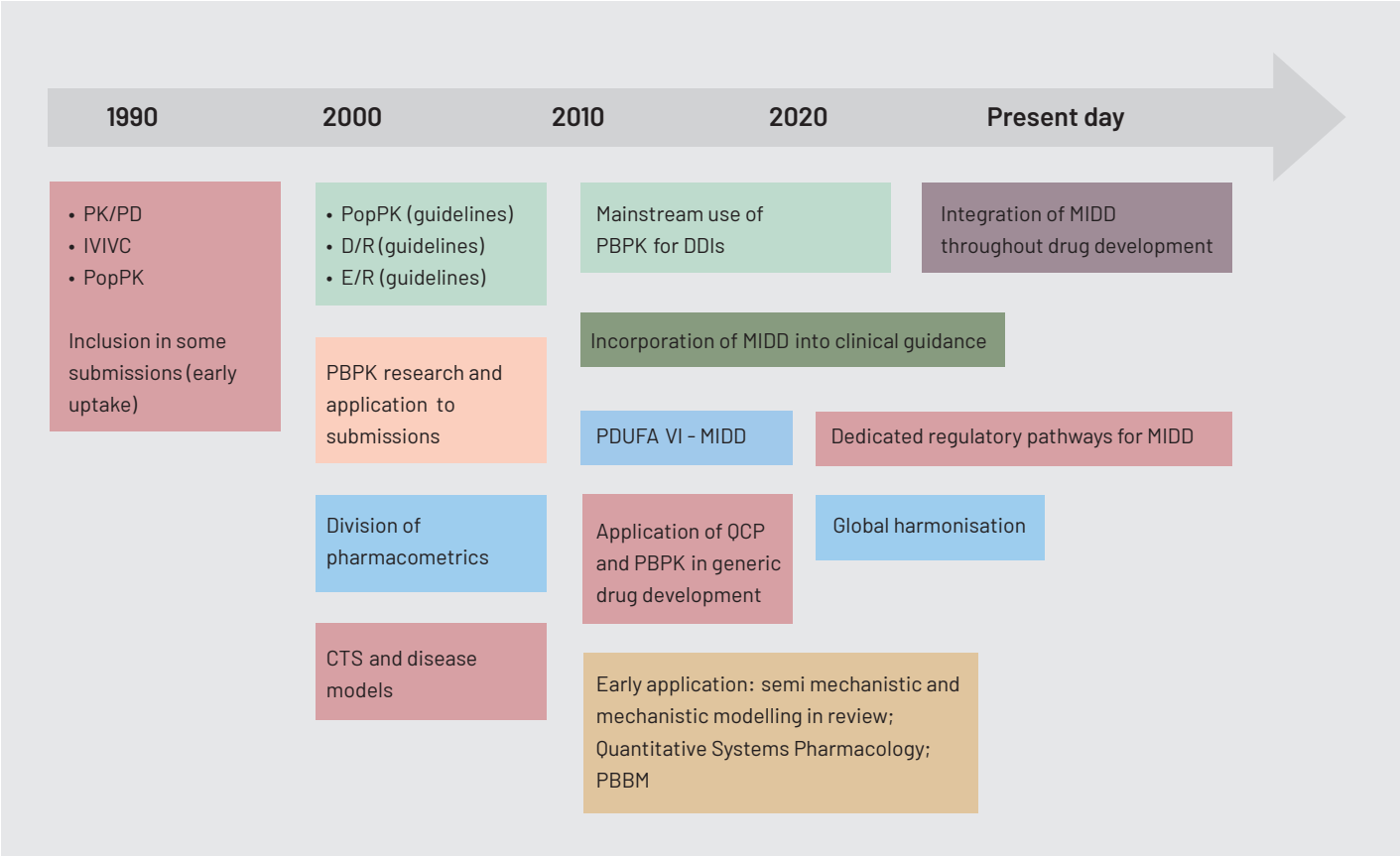

Figure 2. Evolution of MIDD

Abbreviations: CTS, clinical trial simulations; DDI, drug-drug interaction; D/R, dose-response; E/R, exposure-response; IVIVC, in vitro-in vivo correlation; MIDD, model-informed drug development; PBBM, physiologically based biopharmaceutics models; PBPK, physiologically based pharmacokinetics; PDUFA, Prescription Drug User Fee Act; PK/PD, pharmacokinetics/pharmacodynamics; PopPK, population pharmacokinetics; QCP, quantitative clinical pharmacology.

because they target rare diseases.[14] Among the 77 medicines recommended for marketing authorisation by the EMA in 2023, 17 (22%) had a confirmed orphan drug designation.[15] The number of known rare diseases is also increasing, with five new rare diseases described in the literature each month.[8] Therefore, the requirement for experienced medical writers to support regulatory and medical communications in rare disease will grow in the future.

With an inherently small pool of people with a specific rare disease, few patients enrol in clinical trials. Often, it is not possible to run more than one pivotal phase 3 study, and that is usually of a small sample size. There are frequently insufficient data in the early phase studies to inform dose selection for later phase studies, and dose optimisation studies can be unfeasible.[16] Furthermore, the availability of natural disease history data and real-world data is often limited in rare diseases. Both play important roles in defining patient populations, characterising disease progression, and establishing novel biomarkers and clinical endpoints.[17] Maximising the use of all available data about a new product is thus paramount in rare disease drug development, and brings opportunities for MIDD.[18] MIDD approaches allow the integration of all available data, including preclinical studies, controlled clinical trial data, observational data, and aggregated literature data, thereby providing a totality of evidence to enable a more robust characterisation of the risk:benefit profile of the drug.

> Maximising the use of all available data about a new product is paramount in rare disease drug development.

Additional data sources, such as patients' electronic health records, genetic data, and patient registry information, can be leveraged in MIDD to further our understanding of the rare disease and the investigational treatment.[16,19] More importantly, the models allow prediction of responses and inform efficient clinical trial design in diseases with scarce patients.

What does MIDD mean for medical writers?

Development of new drugs for rare diseases is one of the pivotal areas in which quantitative modelling is used extensively. The challenge of generating adequate evidence under conditions of limited information content, such as in rare diseases, has gained visibility over the past two decades. Modelling and simulation are used in all phases of drug development in regions across the world and have historically been used most frequently to support the clinical pharmacology files and labelling for new drug applications. With the expectation of inclusion of modelling in the files from regulators to allow for scrutiny of all available data, marketing applications in the EU and US are rarely submitted without modelling being used to describe the PK of a new medicine, especially in settings in which there is a paucity of clinical data.

Photo: freepik

Currently, medical writers are most likely to come across population pharmacokinetic (PopPK) and pharmacodynamic models, which are the most prominent class of pharmacometric models used in clinical drug development. Familiarity with the documents and outputs associated with this type of modelling, such as PopPK and exposure-response/exposure-safety (ER-ES) analysis reports and plans, is integral for working on rare disease submissions. It is highly likely that medical writers will encounter additional models and associated documents in the near future, so it's important to keep abreast of this rapidly evolving topic.

MIDD is a highly collaborative process, involving not only statisticians and pharmacometricians, but multidisciplinary teams. The role of regulatory medical writers cannot be underestimated given the importance of communicating the results of often complex modelling and simulation exercises to decision-makers and upper management in the pharmaceutical industry, as well as to multidisciplinary review teams within regulatory agencies.[2] MIDD impacts all types of documents that a medical writer may encounter, from protocols to clinical study reports and summary documents, and ultimately product labels.

The role of regulatory medical writers cannot be underestimated given the importance of communicating results of often complex modelling and simulation exercises to decision-makers and upper management.

In addition, the recent draft ICH M15 Guideline[1] refers to modelling analysis plans and reports, as well as MIDD assessment tables, for communication within and between drug developers and regulatory authorities.

Regulatory medical writing requires a style of writing that translates complex medical and scientific information into comprehensive, yet concise and consistent, text. This skill is particularly vital in MIDD, with its complex nomenclature and multifaceted data outputs. Often medical writers with a specific background or interest in PK are the only ones considered for writing the components of the submission involving the explanation of the MIDD and presentation of modelling and simulation data. Especially in light of the increased visibility and emphasis of modelling and simulation in all submissions, challenging yourself and gaining expertise in writing for MIDD could be an area of growth and learning for many regulatory writers, and an important skill set for companies to build within their medical writing groups.

Acknowledgements

The authors would like to thank their Certara colleagues, in particular Steve Sibley and Jen Moyers, for their valuable input.

Disclaimers

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

Disclosures and conflicts of interest

All authors are full-time employees of Certara.

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline. General principles For model-informed drug development M15. Draft 06 November 2024 [cited 2025 Jan 9]. Available from: https://database.ich.org/sites/default/files/ICH_M15_EWG_Step2_DraftGuideline_2024_1031.pdf
2. Lesko LJ. Perspective on model-informed drug development. CPT Pharmacometrics Syst Pharmacol. 2021 Oct;10(10):1127–9.

doi:10.1002/psp4.12699
3. EMA. ICH Topic E 4 Dose response information to support drug registration. May 1994 [cited 2025 Jan 9]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-4-dose-response-information-support-drug-registration-step-5_en.pdf
4. Madabushi R, Seo P, Zhao L, et al. Review: role of model informed drug development approaches in the lifecycle of drug development and regulatory decision-making. Pharm Res. 2022;39(8):1669–80. doi: 10.1007/s11095-022-03288-w
5. Cheung A, Brown F. Essentials of model-informed drug development (MIDD) – Top-down vs. bottom-up approaches [cited 2025 Jan 9]. Available from: https://www.certara.com/blog/essentials-of-model-informed-drug-development-midd-top-down-vs-bottom-up-approaches/
6. Somanadhan S, O'Donnell R, Bracken S, et al. Children and young people's experiences of living with rare diseases: an integrative review. J Pediatr Nurs. 2023;68:e16–26. doi:10.1016/j.pedn.2022.10.014
7. US FDA. Model-informed drug development paired meeting program [cited 2025 Jan 9]. Available from: https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program
8. Baylot V, Le TK, Taïeb D, et al. Between hope and reality: treatment of genetic diseases through nucleic acid-based drugs. Commun Biol. 2024;7(1):489. doi:10.1038/s42003-024-06121-9
9. Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet J Rare Dis. 2023;18(1):163. doi:10.1186/s13023-023-02790-7
10. Institute of Medicine. Rare diseases and orphan products: Accelerating research and development. Washington, DC; The National Academies Press: 2010 [cited 2025 Jan 9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56189/pdf/Bookshelf_NBK56189.pdf
11. National Organization for Rare Disorders. Testimony before the Social Security Administration public hearing on compassionate allowances. Dec 4, 2007. Washington, DC [cited 2025 Jan 9]. Available from: NORDTestimonyCompassionateAllowances120407.pdf
12. National Institutes of Health. Nocardia infection. Reviewed December 4, 2022 [cited 2025 Jan 9]. Available from: http://www.nlm.nih.gov/medlineplus/ency/article/000679.htm
13. Sun W, Zheng W, Simeonov A. Drug discovery and development for rare genetic disorders. Am J Med Genet A. 2017;173(9):2307–22. doi:10.1002/ajmg.a.38326
14. US FDA. Center for Drug Evaluation and Research. Advancing health through innovation: New drug therapy approvals 2023 [cited 2025 Jan 9]. Available from: https://www.fda.gov/media/175253/download?attachment.
15. EMA. Annual Report 2023 [cited 2025 Jan 9]. Available from: https://www.ema.europa.eu/en/documents/annual-report/2023-annual-report-european-medicines-agency_en.pdf
16. Mitra A, Tania N, Ahmed MA, et al. New horizons of model informed drug development in rare diseases drug development. Clin Pharmacol Ther. 2024;116(6):1398–411. doi:10.1002/cpt.3366
17. Liu J, Barrett JS, Leonardi ET, et al. Natural history and real-world data in rare diseases: Applications, limitations, and future perspectives. J Clin Pharmacol. 2022;62(Suppl 2):S38–55. doi:10.1002/jcph.2134
18. Li RJ, Ma L, Li F, et al. Model-informed approach supporting drug development and regulatory evaluation for rare diseases. J Clin Pharmacol. 2022;62(Suppl 2): S27–37. doi:10.1002/jcph.2143.
19. Krishna R, Bullock J. The challenges and opportunities of rare disease drug development [cited 2025 Jan 9]. Available from: https://www.certara.com/white-paper/the-challenges-and-opportunities-of-rare-disease-drug-development/#:~:text=New%20therapeutics%20development%20in%20rare



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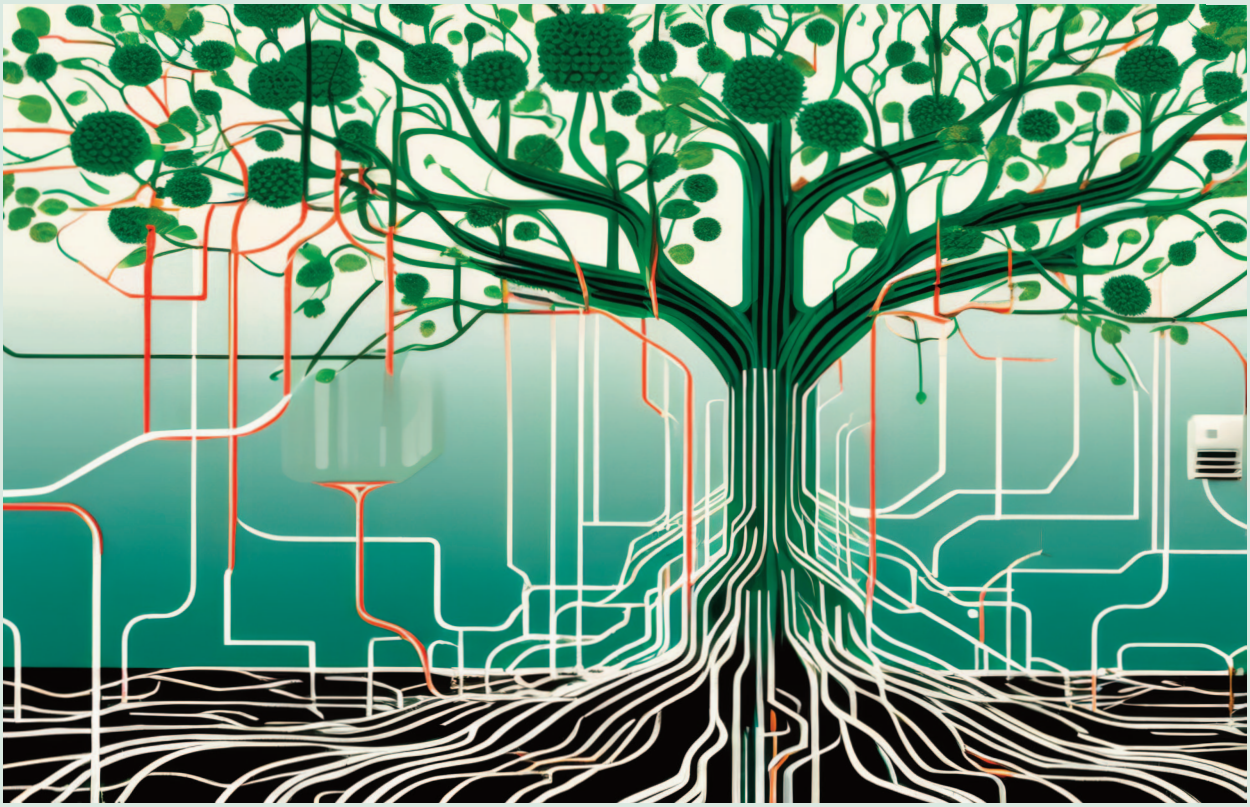

Real world data/ real world evidence

Real-world data and real-world evidence have become integral to medical research and healthcare decision-making. Their value lies in providing insights into how healthcare treatments and interventions perform in everyday settings, which can differ significantly from controlled clinical trial environments. This issue of Medical Writing will include a broad range of articles on the issue theme covering critical aspects for medical writers working with these types of data.

Guest Editor: Maria Kołtowska-Häggström and Laura Collada Alì
The deadline for feature articles is June 1, 2025.

Population diversity in clinical trials for rare diseases:

A regulatory writer's perspective

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Abstract

Ensuring population diversity in clinical trials is essential yet challenging and increasingly complex in the rare disease landscape. The unique challenges in clinical development for rare diseases include limited medical and scientific knowledge, poorly understood natural history data, sample size constraints, and a lack of drug development experience. This article will discuss the evolving regulatory framework for encouraging diversity in clinical trials, explore the unique challenges of applying recommendations within the rare disease landscape, and highlight sustainable solutions for overcoming challenges.

Collage of pics from Freepik

Introduction

Clinical trials are essential to determine whether a medicinal product (hereafter referred to as "drug") works and is safe. Individuals may show varying responses to drugs due to a combination of intrinsic and extrinsic factors. Therefore, it is a regulatory requirement that sponsors of clinical trials assess for unusually large or small responses in population subgroups, for example, examining whether there are any differences by age, sex, and race compared with the overall population.[1] However, historically, the population of clinical trials has been dominated by White males; marginalised racial and ethnic groups, women, and other historically disenfranchised populations have been substantially underrepresented. This makes it impossible to make a comprehensive assessment across an entire affected population who are likely to take the drug, and leaves the clinical relevance on the target population a matter for post-marketing activities.[2] One such case occurred in 2013 when the FDA announced that women who took zolpidem (for insomnia) were at risk for excessive daytime sedation and impaired driving proficiency following bedtime doses. Consequently, the FDA lowered the dose in women as the recommended dose was based on male participants.[3]

> Maximising the use of all available data about a new product is paramount in rare disease drug development.

Over the past few decades, regulatory guidelines on clinical trials have clearly specified that enrolled participants should be representative of the population most likely to use the drug. Nonetheless, homogenous groups continue to overshadow clinical trials, and there is little representation of other characteristics that reflect the target population. This lack of diversity has prompted the EMA and FDA to develop dedicated guidance to address this, which aims to encourage sponsors to design trials that facilitate enrolment of the target population. However, the proposed regulatory strategies have become increasingly complex to implement for many rare diseases, where small populations and unique challenges dominate.

This article will discuss the evolving regulatory framework for encouraging diversity

in clinical trials, explore the unique challenges of applying recommendations within the rare disease landscape, and highlight sustainable solutions for overcoming these challenges.

Regulatory framework

The regulations around diversity in clinical trials are evolving. The Clinical Trial Regulation No 536/2014,[4] which governs clinical trials in the EU, reinforces the requirement that participants should represent the population the drug is intended for, and has a clear emphasis on age and sex. There is an expectation that sponsors must provide a justification if a trial does not reflect the target population. However, there is no reference to race, keeping ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data[5] the primary guidance for evaluating the impact of ethnic factors. There is no expansion on considering intrinsic and extrinsic factors when designing trials, in view of the EMA adopted guidance ICH E17 Multi-Regional Clinical Trials.[6] ICH E17 recognises that differences in medical practice, diet, environmental factors, cultural or socioeconomic factors (e.g. contraceptive use, preferences for a particular route of administration), geographic location, and access to healthcare can impact trial results. These factors may also impact recruitment, compliance, and participant retention.

> Over the past few decades, regulatory guidelines on clinical trials have clearly specified that enrolled participants should be representative of the population most likely to use the drug.

The regulations in the USA have developed considerably over decades. In 2013, an FDA report to Congress highlighted demographic data gaps, which birthed the Diversity Action Plan.[7] This plan provided recommendations to standardise data collection, improve data quality and public availability, ensure demographic representation, and consider the integration of diversity throughout a drug's lifecycle.

The plan was reflected in the FDA Guideline on Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products Guidance for Industry, 2016,[8] which gives an update on a standardised approach to collecting and reporting race and ethnicity data. It recognises that "race and ethnicity categories are not anthropologically or scientifically based designations, but instead are categories that describe the sociocultural construct of our society", highlighting the importance of considering additional factors when designing trials. The significance of collecting comprehensive demographic data has been emphasised in a June 2024 revision to "Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products Guidance for Industry," to promote the inclusion of race and ethnicity information in the proposed product labelling by providing the baseline demographics of the study population in the Clinical Studies and Adverse Reactions sections.[9]

To unequivocally encourage population diversity in clinical trials, the FDA issued "Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry, 2024".[10] This guidance focuses on increasing the enrolment of underrepresented populations, underscoring the necessity of considering demographic characteristics (e.g. sex, race, ethnicity, age, location of residency) and non-demographic characteristics of populations (e.g. patients with organ dysfunction, comorbid conditions, disabilities, those at the extremes of the weight range, and populations with diseases or conditions with low prevalence). It primarily recommends broadening study eligibility criteria and using study designs to reduce participant burden to "create a study population that more accurately reflects the patients likely to take the drug if it is approved, and allow assessment of the impact of those characteristics on the safety and effectiveness of the study drug."[10]

To actively engage sponsors, the FDA issued a draft guidance titled "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies,"[11] which referred to a new document (Diversity Action Plan) that sponsors should submit to show the plan for enrolling a diverse population into certain late-stage clinical trials. While population diversity is often viewed after enrolment by evaluating the demographic and baseline characteristics of the study results, the Diversity Action Plan will ensure the following are purposely well-thought-out prior to enrolment: a. enrolment goals by race, ethnicity, sex and age, b. the rationale for enrolment goals, and c. measures to meet those goals.

However, in January 2025, days after US President Trump issued an executive order to terminate federal diversity, equity, and inclusion programs, the FDA quietly removed the draft guidance "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies" from their website. This apparent act of dismantling is concerning and raises questions about the FDA's commitment and the applicability of statutory obligations for sponsors to submit Diversity Action Plans.

Rare diseases

The EMA defines a disease as "rare" if it affects less than 5 in 10,000 people in the EU.[12] Rare diseases impact more than 400 million people worldwide, yet most conditions have no approved treatment. Clinical development in the rare disease landscape is complex as there is often limited medical and scientific knowledge, poorly understood natural history data, sample size constraints, and a lack of drug development experience.[13] Population diversity in a trial becomes increasingly challenging with the added complication of affecting only small, geographically dispersed populations.[13] However, diversity is vital to ensure results are safe and applicable to the general population.

Challenges with increasing diversity in rare disease clinical trials

Broadening eligibility criteria

> Diversity is vital to ensure results are safe and applicable to the general population.

Rare diseases are highly diverse, with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease courses within a condition, and little is known about a disease's natural history and pathophysiology.[13] Because of this, the study eligibility criteria in clinical trials for rare diseases are often narrow to limit variability.

One of the key regulatory approaches to increasing the enrolment of a diverse population is to broaden the eligibility criteria of the clinical

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trial.[11] While this approach may satisfy an increase in diversity, broadening it too extensively could increase variability, complicating the interpretation of trial results.

Sample size

Conducting clinical trials for rare diseases is inherently challenging because of the small number of available participants. A recommended regulatory approach to increase diversity is to increase the proportional enrolment of specific populations of interest. However, this is not feasible for many rare diseases, where populations are small and enrolment is slow.

Ways to increase diversity in clinical trials for rare diseases

Adaptive trial designs

A clinical trial designed to allow prospectively planned modifications to one or more aspects of the trial based on interim results is described as having an adaptive design. Adaptive trial designs can provide a variety of advantages in the rare disease landscape as they allow adjustments to information that was not available at the start of the trial.[14]

By using an adaptive design, a trial can be planned that allows modifications to the study eligibility criteria following interim results. This flexibility could permit the inclusion of underrepresented groups who may have initially been excluded because of narrow eligibility criteria and enable the trial to reflect better the diverse population likely to take the drug.

Another adaptive approach is a study designed to prospectively plan modifications to the sample size based on interim results.[11] If certain groups are underrepresented early in the trial, and it is possible to increase the sample size considering the rarity of the disease, recruitment could target specific groups.

Adaptive trial designs can provide a variety of advantages in the rare disease landscape as they allow adjustments to information that was not available at the start of the trial.

Community engagement

Research has identified many barriers to the inclusion of diverse populations in clinical trials, which can be buried within the rare disease community. Participants from marginalised communities often mistrust the pharmaceutical industry, fear exploitation, lack awareness of their disease or of available trials, and have language barriers or operational constraints.[15] Concurrently, sponsors may have limited commitment and effort, conduct centralised studies, lack culturally or racially diverse staff, lack community engagement, and have negative attitudes about willingness from marginalised communities.[15]

Patient advocacy plays an instrumental role in clinical trial development for rare diseases. To increase enrolment of historically underrepresented populations, sponsors may strengthen community engagement by providing cultural competency training for clinical investigators and site staff to better engage with participants from different backgrounds, streamline informed consent where risks are low, provide patient leaflets in multiple languages, and provide language assistance for participants with limited English proficiency.[15]

Decentralised trials

Traditionally, clinical trials have been conducted at specific clinical trial sites. However, the burden this can have on participants is well-recognised, and regulatory guidance has been developed to facilitate the conduct of decentralised clinical trials.[16] Decentralising clinical trials will allow some or all trial-related activities to take place at trial participants' homes or other convenient locations instead of having them visit research sites, and include options such as an electronic informed consent.[17] Reducing barriers to participation may increase the diversity of participants with rare diseases, and improve accessibility and retention.

Conclusion

Population diversity in clinical trials is essential; however, it poses unique challenges for rare

diseases. The regulatory guidance encourages sponsors to do better, but many trials are not yet enrolling a diverse population that is reflective of the target population. By leveraging adaptive study designs, culturally tailoring patient engagement, and decentralising trial sites, sponsors can be equipped with strategies to increase population diversity in rare disease trials, which is both an ethical and scientific necessity. However, with recent cracks in regulatory legislation, there are concerns about the commitment from authorities, the obligation of sponsors, and the acknowledged importance of clinical trial diversity and health equity.

Acknowledgements

The author would like to thank Dr Heather L. Mason for supporting the development of this article and for content review and editorial assistance.

Disclaimers

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

Disclosures and conflicts of interest

The author is employed by BioMarin Pharmaceutical. The author declares no conflicts of interest.

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH E3 guidelines: Structure and content of clinical study reports. Available from: https://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
2. Clark LT, Watkins L, Piña IL, et al. Increasing diversity in clinical trials: overcoming critical barriers. Curr Probl Cardiol. 2019;44(5):148–72. doi:10.1016/j.cpcardiol.2018.11.002
3. Greenblatt DJ, Harmatz JS, Roth T. Zolpidem and gender: are women really at risk? J Clin Psychopharmacol. 2019;39(3):189–99. doi:10.1097/JCP.0000000000001026
4. European Commission. Clinical trial regulation (EU) No 536/2014 [cited 2025 Jan 02]. Available from: https://ec.europa.eu/health/human-use/clinical-trials_en
5. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data. 1998 [cited 2025 Jan 02]. Available from: https://www.ich.org/page/efficacy-guidelines
6. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH E17: General Principles for Planning and Design of Multi-Regional Clinical Trials. 2017 [cited 2025 Jan 02]. Available from: https://www.ich.org/page/efficacy-guidelines
7. US FDA. FDA action plan to enhance the collection and availability of demographic subgroup data [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/89307/download
8. US FDA. Collection of race and ethnicity data in clinical trials: Guidance for industry and FDA staff. 2016 [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/75453/download
9. US FDA. Collection of race and ethnicity data in clinical trials: Guidance for industry and FDA staff. 2024 [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/175746/download
10. US FDA. Enhancing the diversity of clinical trial populations – eligibility criteria, enrollment practices, and trial designs: Guidance for industry. 2020 [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/127712/download
10. US FDA Diversity Action Plan [cited 2025 Jan 02]. Available from: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies Guidance for Industry (Draft) 2024 [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/179593/download
11. EMA. Orphan designation: Overview [cited 2025 Jan 02]. https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview
12. US FDA. Rare diseases: Considerations for the development of drugs and biological products. Guidance or industry [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/119757/download
13. US FDA. Adaptive designs for clinical trials of drug and biologics. Guidance for industry [cited 2025 Jan 02]. Available from: https://www.fda.gov/media/78495/download
14. Reopell L, Nolan TS, Gray DM II, et al. Community engagement and clinical trial diversity: navigating barriers and co-designing solutions – A report from the "Health Equity through Diversity" seminar series. PLoS One. 2023;18(2):e0281940. doi:10.1371/journal.pone.0281940
15. EMA. Facilitating decentralised clinical trials in the EU [cited 02 Jan 2025]. Available from: https://www.ema.europa.eu/en/news/facilitating-decentralised-clinical-trials-eu
16. US FDA. FDA takes additional steps to advance decentralised clinical trials [cited 02 Jan 2025]. Available from: https://www.fda.gov/news-events/ press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials#:~:text=Today%2C%20the%20U.S.%20Food%20and,than%20traditional%20clinical%20trial%20sites.

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How can real-world data, registries, and databases address the challenges of rare diseases?

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doi: 10.56012/kwle5627

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Abstract

A goal for all diseases is a treatment that works to prevent, halt, or reverse their effects – essentially, a cure. Achieving this requires early diagnosis, knowledge of disease mechanisms, and effective treatment. For rare diseases, each of these elements is a huge challenge. This perspective explores how real-world and registry data can address these obstacles and considers future developments with the potential for the most significant impact.

A goal for all diseases is a treatment that works to prevent, halt, or reverse their effects – essentially a cure. The quest to understand and treat rare diseases is among the most challenging and vital missions in healthcare today. In Europe, over 20 million people live with a rare disease, with about 75% affecting children under the age of 2 years, and more than 260 million people are affected worldwide, about 5% of the total population.[1] A disease is classed as rare if it affects less than 5 in 10,000 or 1 in 2,000 of the European population, or fewer than 200,000 people in the USA. There are over 6,000 rare diseases, many of which are life-limiting and lack effective preventative or curative treatment. These are often inherited metabolic diseases and so can affect several children within a family. For ultrarare diseases, only a few families may be diagnosed.

In this perspective, we highlight the need for real-world evidence and registries that capture patient data and summarise how these can address the specific challenges of rare diseases.

Core concepts of real-world evidence and registries in the context of rare diseases

For common diseases affecting many people, it is relatively easy to collect data about the disease and to find enough people willing to participate in clinical trials. However, this is not the case for rare diseases. Therefore, real-world data (RWD) is an essential source of information for rare diseases and can help with diagnosis, treatment development, clinical management, and research.[2] Essentially, RWD is a collection of patient health-related data. This is most useful when held in electronic format to allow processing by codifying to aid analysis. RWD can include data from patient registries and hospital records, including regular checkups and other sources such as wearable devices, smartphones, and information provided by patients or disease registries.

RWD can provide information on disease prevalence, incidence, and natural history and can be used for scientific health research and public health purposes. RWD can be either structured, such as laboratory orders, prescriptions, and lists of procedures; semi-structured, which includes digital images that contain structured attributes like device identification and DateTime stamp; or unstructured, such as clinical progress notes, pathology reports, radiology reports, patient correspondence, and insurance letters. Unstructured data has a lot of richness due to its diverse, variable, and sometimes unpredictable nature, but it is not easy to code and analyse.

RWD can provide information on disease prevalence, incidence, and natural history and can be used for scientific health research and public health purposes.

Codifying RWD into electronic format so that it can be analysed has huge potential. Machine learning with clinical narratives containing deep and detailed phenotypes can recognise new patterns across the whole group of patients and tie these to individual patients to estimate disease activity, including progression and remission and recognition of different disease subtypes.[3] This can give a clearer picture of a patient's history, provide more details about disease trajectory, and provide early warning signs for adapting care, an emerging critical clinical event, or even a new diagnosis. It can be powerful to link a problem needing a solution with real-world evidence (RWE) and artificial intelligence (AI).

Patient registries have been set up for many rare diseases to gather information required for treatment development in one place. There are different types of patient registries.[4] These can be based on a single or group of related diseases, assembled to gather data to test a new product in a clinical trial, or draw data from a particular population. Registries may be set up either by pharma developing a product and restricting the data for internal use or by patient organisations or clinical consortia, in which case the data may be available for others to use.

The scientific evidence derived from analysing RWD is called real world evidence (RWE). For example, gathering and analysing clinical evidence of the benefits or risks of a new medicinal product is RWE. It can be used to support regulatory purposes, such as the first applications for marketing authorisations for orphan medicines. In this way, RWD and RWE can be used to bring new therapies to patients.

Data from clinical trials are prospectively obtained with a predetermined purpose and often from a specially determined and limited group of similar patients. However, RWD is observational, can be large in size, and is frequently drawn from a variety of patient backgrounds. Therefore, RWD can be messy,

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incomplete, and subject to bias. RWD complements traditional clinical research data. Equally, RWD can consolidate knowledge from data that may not be collected during clinical trials, such as the impacts of economic and social factors and the quality of life of patients with rare diseases. These additional data further enhance the evidence-based decisions made when bringing new medicines to patients, especially as waiting for the next trial may be too late for some.

Unique challenges of rare diseases

People with rare diseases are scattered across the globe, and so is their data. The collection of such data and its use is vital and challenging, partly because of its scarcity but also the heterogeneity of the patient population. Gathering RWD, especially those collected during daily life, may reduce the number of hospital visits and avoid the need to relocate during a clinical trial, which has massive implications on family life and resources. Designing a clinical trial to include RWD can benefit families, although there are concerns about the quality and comparability of RWD with randomised clinical trial data.

There is limited knowledge across many aspects of some rare diseases, especially ultrarare ones, from their natural history to patho-mechanisms and correlations between genotype and phenotype. Rare diseases often face delays in diagnosis due to the time taken to first rule out more common diagnoses. Specialised tests may be needed for confirmation, but these are not available to all patients around the globe.

Patient heterogeneity arises from the underlying genetic cause in allelic diseases. In some, this results in a complete loss of function of a single disease gene; in others, the retention of partial function is due to genetic variation such as missense mutations. Heterogeneity may additionally reflect other genomic influences beyond the disease gene, and environmental factors such as diet and living conditions, which vary globally. Patient registries that include genetic variation data can be invaluable here.

> Unstructured data has a lot of richness due to its diverse, variable, and sometimes unpredictable nature, but it is not easy to code and analyse.

Benefits of patient registries

There are many benefits of setting up patient registries to provide RWD. They provide information on the natural history of a rare disease, the incidence, the expected numbers of patients eligible for a clinical trial, the choice of endpoints in clinical trial design, tracking treatment outcomes, quality of life assessments which lead to healthcare resource utilisation, and post-market surveillance once a new medicine is available in the clinic. For rare diseases, this has led to the recognition that no group needs to receive placebo treatment during clinical trials. Collection of RWD might reveal unmet care needs that can then be addressed. During expanded clinical trials, RWE provides information on treatment efficacy in patients who may differ in their genetic variation or support settings. RWE supplements the more restricted early clinical trials, typically involving only a small number of patients.

Best practices and examples of registry design

The holding of personal data, including health data, is regulated, creating challenges in sharing this data as regulations are different worldwide. Families with rare diseases are often very willing to allow the collection of their data, as they understand its importance in research and development. For registries to provide RWD, they require quality assurance processes for data organisation, data quality, consideration of potential biases, and for the database to be fit for purpose.

Photo: freepik

A recent survey identified many rare disease registries,[5] with most based in Europe, predominantly led from Germany, the UK, or the USA. Some hold more than 30,000 cases. Two-thirds cover a range of diseases, and a third only one disease. Most are national, with many others continental or global, which requires interoperability in terms of data elements ontologies, and common terminologies to allow data collected in different places to be combined. They aim to provide participants for clinical studies, to evaluate or improve clinical care, to describe epidemiology, or to improve understanding of the natural history. Data collected includes sociodemography, diagnosis, medical history, care pathway, and treatment history. Approximately one-fifth of registries use common or core data or ontological coding language, which considers what the data is about, defines variables, and translates the data to create standardised terms for global use. Nearly half have no clear governance. Many include patient-reported outcomes, but not all involve all potential users, such as patient organisations, in their design. Funding came mainly from federal or European Union bodies, with many funded by private pharmaceutical or technical companies.

> The age of onset is distinguishable from the age of diagnosis, given that the time between these may be considerable.

One example of a rare disease registry is Sanofi's Rare Disease Registries,[6] which was set up 30 years ago and expanded to collect data on rare lysosomal storage disorders (LSDs) (Fabry, Gaucher, Mucopolysaccharidosis type I, and Pompe disease). This registry contains data from over 18,000 patients who have one of these four LSDs and are enrolled at over 800 sites in 64 countries. There is now a Rare Disease Registries Patient Council, which is leading to further improvements. This RWD has led to more than 100 peer-reviewed articles published to advance learning on these diseases.[7]

Another example from our personal experience is DEM-CHILD, a patient registry for neuronal ceroid lipofuscinoses (NCL), also known as Batten disease. This registry was initiated by collaborating European clinicians and led by Dr Angela Schulz to improve early diagnosis and optimise standards of care.[8] DEM-CHILD registers patients with different forms of NCL to measure the prevalence of each type of NCL in participating countries. It collects retrospective and prospective patient data to precisely describe the clinical course and its variability in the different forms of NCL, correlating patients' genotypes with their phenotypes by linking clinical and genetic mutation data. DEM-CHILD also provides a tool for evaluating experimental therapy studies and palliative therapies. The registry currently has over 250 patients in the database.

DEM-CHILD follows best practices for registry design, with ethical approval, and it follows European data protection guidelines. There is an approved audit trail to ensure data safety, and the data is stored on different servers with emergency power supply and daily backup.

Since its founding, improvements have been made, and there are plans to allow parents to contribute data. The registry harmonises data collection and sharing and facilitates non-exclusive data sharing with third parties globally,

such as scientists and pharma. This supports the development of various therapies and the collection and sharing of patient samples with third parties. Established and novel clinical rating scales have been applied to assess disease progression for different NCL types, and quality-of-life questionnaires utilised. Clinical assessments are comprehensive for both the central nervous system (CNS) and extra CNS disease manifestations. A collection of serum and cerebrospinal fluid samples is available in the associated DEM-CHILD biobank.

A mark of its success is that the EMA and the FDA accepted the natural history data held in DEM-CHILD for late infantile CLN2 disease as valid natural-history controls for the efficacy evaluations in experimental therapies for CLN2 disease. This led to an expedited approval of intracerebroventricular enzyme replacement therapy with cerliponase alpha in May 2017.[9-11] There are other examples of similar successes utilising rare disease registries.[12]

There is a need to understand genetic variation and how this correlates with disease progression. In parallel with DEM-CHILD, the NCL-Resource contains the freely accessible NCL Mutation Database. This curated database collects published data on the genetics and phenotype of NCL patients and gathers this data in one place. The data inspires scientific design and can be used to predict disease severity and consider implications for therapeutic development.[13-15] More than 700 genetic variations in NCL genes are currently captured, together with details from more than 1,700 patients. The curation focuses on data quality and accuracy. For example, potentially duplicated patient records are highlighted and investigated further with relevant clinicians or researchers. The age of onset is distinguishable from the age of diagnosis, given that the time between these may be considerable. Each variant is checked for accurate Human Genome Variation Society nomenclature for the patient's genetic information. Errors in variant nomenclature are relatively common and, in some cases, have led to the publication of purported new variants when, in reality, they are misdescribed known variants. Thus, for the NCL database, consistent application of several checks by an expert curator increases the quality and accuracy of its data.

Emerging digital health technology allows the capture of digital biomarkers in a home-based disease assessment, which can be expected to provide more consistent RWD than a visit to an unfamiliar clinic. One example is the use of video capture to assess a key transition stage in the loss of independent walking but retention of weight bearing and transfer in the development of Duchenne muscular dystrophy. Such computer vision analysis can extract objective, quantitative measures, including time, movement trajectory patterns, and movement smoothness and symmetry, to identify voluntary or compensatory movements that can mark disease progression. Such RWD could inform clinical endpoints and be used in future clinical trials.[16]

The contribution of medical writing

Professional medical communication writers translate complex information into content that is more accessible in terms of clarity and appropriate for different platforms and target audiences. With respect to RWE and registry data, one important contribution is to enable those who are less familiar with the underpinning medical and scientific concepts to understand their importance and potential. This may allow patients to make an informed decision on whether to give permission for their medical data to be incorporated into a registry or to be analysed, or medical and allied professionals within the rare disease field to appreciate the potential of analysis of medical data and to contribute to this. Further, this requires working closely with those who run the registries and produce the RWE and who are ultimately responsible for driving the accessibility of this impactful research.

Conclusions and future perspectives

We have highlighted the contribution that RWD and registry data are already making towards effective treatments for rare diseases. As the industry seeks innovative solutions, RWE studies utilising RWD have grown in acceptance.[17] It has been argued by many that RWD provides valuable insight into how an investigational medicinal product performs in the real world. In contrast, a randomised controlled trial setting is heavily regulated, with robust patient inclusion and exclusion criteria defined in an approved protocol and trial settings. Therefore, RWD can provide insight that cannot be obtained through traditional means, and it brings in other patient populations that may have been overlooked, so it should not be ignored. This paradigm shift from traditional clinical data to real-world insights marks a new era for researchers, physicians, and patients alike. As the industry adapts, the implications of RWD are revealed, shaping the future of diagnosis, treatment, and patient care.

We suggest that every rare disease should be linked with a registry, and each should be standardised as necessary to offer the best practice for capturing global RWD. Access to this RWD should not be restricted unnecessarily. RWD provided by digital health technology could be improved by home-based regular longitudinal assessments appropriate to the disease. This will increase the potential of AI, including machine learning, to highlight key disease markers beyond clinical markers and open both contributions of data and clinical trials to patients around the world who do not have ready access to specialised centres of clinical excellence. Additionally, all registries should be fit for use by regulatory bodies.[17]

Finally, this perspective is written for medical writers. With their clear writing, these professionals can reach medical engineering professionals, young scientists, and future clinicians who may not yet be reading scientific publications and medical journals to inspire them to contribute to this area of work.

Acknowledgements

The authors thank all those who contribute to disease registries and databases, research publications, and case reports from which NCL mutation data is drawn. This work was supported by an award from the UK Medical Research Council (MR/V033956). Sara Mole (ORCID: 0000-0003-4385-4957) reports support by Biomarin for maintaining the NCL mutation database curated by Emily Gardner. All research at Great Ormond Street Hospital National Health Service (NHS) Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the National Institute for Health and Care Research (NIHR) Great Ormond Street Hospital Biomedical Research Centre.

Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Disclosures and conflicts of interest

The authors declare no conflicts of interest.

References

1. Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020;28(2):165-73. doi:10.1038/s41431-019-0508-0
2. Liu F, Panagiotakos D. Real-world data: a brief review of the methods, applications, challenges and opportunities. BMC Med Res Methodol. 2022;22(1):287. doi:10.1186/s12874-022-01768-6
3. Jefferies JL, Spencer AK, Lau HA, et al. A new approach to identifying patients with elevated risk for Fabry disease using a machine learning algorithm. Orphanet J Rare Dis. 2021;16(1):518. doi:10.1186/s13023-021-02150-3
4. Pisa F, Arias A, Bratton E, et al. Real world data for rare diseases research: the beginner's guide to registries. Expert Opin Orphan Drugs. 2023;11(1):9–15. doi:10.1080/21678707.2023.2241347
5. Hageman IC, van Rooij IA, de Blaauw I, et al. A systematic overview of rare disease patient registries: challenges in design, quality management, and maintenance. Orphanet J Rare Dis. 2023;18(1):106. doi:10.1186/s13023-023-02719-0
6. Mistry PK, Kishnani P, Wanner C, et al. Rare lysosomal disease registries: lessons learned over three decades of real-world evidence. Orphanet J Rare Dis. 2022;17(1):362. doi:10.1186/s13023-022-02517-0
7. Sanofi. Real-world evidence requires real-world patients. 2024 [cited 2025 Jan 03]. Available from: https://www.sanofi.com/en/magazine/your-health/real-world-evidence-requires-input-from-real-world-patients.
8. Schulz A, Simonati A, Laine M, et al. The DEM-CHILD NCL Patient Database: A tool for the evaluation of therapies in neuronal ceroid lipofuscinoses (NCL). Eur J Paediatr Neurol. 2015;19- Suppl 1: S16. doi:10.1016/S1090-3798(15)30049-0
9. Schulz A, Ajayi T, Specchio N, et al. Study of intraventricular cerliponase alfa for CLN2 disease. N Engl J Med. 2018;378(20):1898–907. doi:10.1056/nejmoa1712649
10. Nickel M, Simonati A, Jacoby D, et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. Lancet Child Adolesc Health. 2018;2(8):582–90. doi:10.1016/s2352-4642(18)30179-2
11. Nickel M, Schulz A. Natural history studies in NCL and their expanding role in drug development: Experiences from CLN2 disease and relevance for clinical trials. Front Neurol. 2022;13:785841. doi:10.3389/fneur.2022.785841
12. Liu J, Barrett JS, Leonardi ET, et al. Natural history and real-world data in rare diseases: applications, limitations, and future perspectives. J Clin Pharmacol. 2022;62(Suppl 2):S38–55. doi:10.1002/jcph.2134
13. Gardner E, Bailey M, Schulz A, et al. Mutation update: review of TPP1 gene variants associated with neuronal ceroid lipofuscinosis CLN2 disease. Hum Mutat. 2019;40(11):1924–38. doi:10.1002/humu.23860
14. Gardner E, Mole SE. The genetic basis of phenotypic heterogeneity in the neuronal ceroid lipofuscinoses. Front Neurol. 2021;12:754045. doi:10.3389/fneur.2021.754045
15. Lourenco CM, Pessoa A, Mendes CC, et al. Revealing the clinical phenotype of atypical neuronal ceroid lipofuscinosis type 2 disease: insights from the largest cohort in the world. J Paediatr Child Health. 2021;57(4):519–25. doi:10.1111/jpc.15250
16. Ferrer-Mallol E, Matthews C, Stoodley M, et al. Patient-led development of digital endpoints and the use of computer vision analysis in assessment of motor function in rare diseases. Front Pharmacol. 2022;13:916714. doi:10.3389/fphar.2022.916714
17. Giannuzzi V, Stoyanova-Beninska V, Hivert V. Editorial: The use of real world data for regulatory purposes in the rare diseases setting. Front Pharmacol. 2022; 13:1089033. doi:10.3389/fphar.2022.1089033

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On orphans and zebras

The adjective "**orphan**" is used metaphorically to denote "without" something important. In bioscience, examples include:

- *"An orphan virus, such as hepatitis G, is one without a recognised associated disease.*
- *Orphan enzymes have catalytic sites that can be occupied by millimolar concentrations of ethanol but have no known physiological roles.*
- *Orphan receptors, such as the opioid OP4 receptor identified from gene sequences, have no known endogenous ligands or physiological functions."*[1]

Orphan diseases, sometimes called neglected diseases, are conditions that have no or limited treatment options. The main reason for this omission is that development of such treatments is not considered profitable. Rare diseases are a subset of orphan diseases, and their neglect is mainly due to the limited patient population. Not all orphan diseases are rare.

Zebras are neither rare nor neglected. So why is the zebra used as symbol for rare diseases? It was supposedly based on a common saying in the medical world "*When you hear hoofbeats behind you, don't expect to see a zebra.*" Attributed to the American medical researcher Dr Theodore Woodward,[2] the mantra advocated to look for the most obvious answers in the field of diagnostics. In the rare disease space, however, the zebra represents that out-of-the-box "Dr House" thinking that led to the diagnoses of many less known diseases.

Reference:

1. Aronson J. Rare diseases, orphan drugs, and orphan diseases. BMJ. 2006;333(7559):127. doi:10.1136/bmj.333.7559.127
2. Why the zebra? CACP Research Foundation. Available at: https://www.cacpresearchfoundation.org/why-the-zebra#:~:text=When%20examining%20the%20symptoms%20of,disorders%20are%20actually%20not%20rare

Rare Disease spotlight

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Penning hope: The impact of medical writing for rare conditions

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Abstract

In this article, I explain my route into the world of rare conditions, my experience of working as a clinician, and my passion for raising awareness to all involved. I achieve this by providing education to healthcare professionals, patients, and patient advocates in low- and middle-income countries. I also discuss the vital role that medical writers have played in this mission.

Introduction

I qualified as a medical doctor in South Africa in 1985 from the University of Pretoria, where I also completed my master's degree in Sports Medicine. Following a rare disease diagnosis of my youngest child, I moved to the United Kingdom to continue my studies, becoming an expert in inborn errors of metabolism in paediatric and adult care.

I became a Member of the Royal Society of Physicians (MRCP) and a Fellow of the Royal Society of Paediatrics and Child Health (FRCPCH), with subspecialty registration after training at the world-renowned Willink Unit in Manchester, UK.

After spending more than 20 years as an academic, clinician, and researcher, I am now the Chief Community Impact Officer for A Rare Cause, a non-profit organisation based in England that educates clinicians on rare disease management in more than 50 countries, with the list growing annually. This creates hope for those with the least chance of being recognised.

Misunderstood and of no importance

Rare diseases and medical writing are often misinterpreted and undervalued. This article will explore the significant yet frequently overlooked impact that both have on the scientific community and society, highlighting my personal journey with each.

My more than 20 years of experience in rare disease management was triggered by the journey with our youngest child, who has a rare disease. During this journey, I made many acquaintances who became true friends, made up of medical professionals, patient organisations, pharmaceutical industry colleagues, and medical writers (MWs).

My first introduction to medical writing was very early in my career after I presented an awareness programme to a public audience. The MW connected with me afterward and said that they had really enjoyed my presentation, and that, although it was not their place, they wanted to provide some constructive feedback. I learned about MWs' skills in making presentations more visually attractive and using infographics to explain complex concepts. Their advice became very important later when I wanted to develop patient-friendly communications.[1]

> Through my experience, I've found that the most effective medical writers are those who have been exposed to the rare disease community and understand its unique issues.

Through my experience, I've found that the most effective MWs are those who have been exposed to the rare disease community and understand its unique issues.[2] The unique challenge of medical writing for the rare disease community lies in the rarity of these conditions and the lack of extensive evidence. Consequently, the patient's perspective and input become especially important. The patients and families are also usually very knowledgeable about their condition and the impacts of the disease on family life and the wider community. MWs will usually have a science background, which would help them engage with the community, but this is the time to be humble, listen, and get a true insight into the frustrations and challenges of the community. Then follows the understanding of working with small groups, unique clinical trial designs, and the lack of any minimally clinically important (MCI) outcomes or validated tools, which are usually required in scientific publications. MWs are in a unique position to highlight these issues and help develop publications to support the MCI differences (MCID) in rare disorders.[3] Being involved in this community is becoming part of the solution. I will share examples of how this became a reality in my journey through rare diseases and the benefit of rare disease medical writing champions.

While working for the National Health Service, our interactions with MWs were primarily related to post-approval registry studies. Our medical writing colleagues brought valuable experience from the pharmaceutical industry to these projects. They had a vital role in the management of the registries by creating templates and online tools that helped streamline communication and collaboration, ensuring that the projects progressed smoothly. MWs may also be involved in setting up the kick-off and comment resolution meetings, developing the timelines, and ensuring alignment with industry guidance, for example, the International Committee of Medical Journal Editors' criteria for determining authorship.[4] They play a crucial role as intermediaries between the pharmaceutical industry and the egos of key opinion leaders. Their goal is to ensure that data is collected and presented in an accessible format, ultimately benefiting patients and non-expert readers.

In industry and early clinical development, regulatory medical writers specialising in rare diseases are once again invaluable. Some of the routine tasks, such as template development, formatting, submission guidance, and compliance with copyright, are no different from those for more common disease areas. Still, a regulatory MW experienced in the field will frequently identify gaps for developers. Some simple examples are: the submission for orphan designations and the tools and methods to calculate prevalence data for rare diseases; the ability to obtain Rare Disease Paediatric Vouchers and how these support pipeline development;[5] and posing critical questions during the synopsis/ protocol development phases, for example, "Have you heard about this option?" or "Have you seen this before working with another partner?". This interaction between MWs and early clinical trial developers brings added value, which can only be provided by those with expertise in the rare disease space.

This interaction between MWs and early clinical trial developers brings added value, which can only be provided by those with expertise in the rare disease space.

Medical writers can be patient advocates

Working on rare diseases in low- and middle-income countries (LMICs) is complicated, and having the voice of an impartial medical writer brings perspective and additional benefits. MWs can bring knowledge about working on different platforms and how low-cost measures like free or charitable collaboration platforms and virtual tools can be used to connect groups to build networks.

We started a very ambitious project called the Africa Roadmap project to build a clinical diagnostic network for those in Sub-Saharan Africa.[6] This was a joint project between multiple partners, including academia, patient organisations, laboratories, and charitable programmes. There was no funding to support medical writing, but on a pro bono basis, our MW colleagues provided advice and guidance on strategies to support the project. The Africa Roadmap project has now connected 10 Sub-Saharan countries, with more to come. Although the need for medical writing is well appreciated by those in high-income countries, it is still perceived as a luxury add-on in this context rather than an integral partner, and this is a genuine gap that needs to be filled in the future. Having MW experts help develop culturally appropriate medical guidelines and patient-friendly medical communications will become more important as this field develops. We have been able to create patient-friendly guidelines for high-income countries, but this should also become a reality for those less privileged. We frequently push the pharmaceutical industry to show some social responsibility by supporting charitable access programmes, but as there is no perceived financial benefit from these programmes, only a select few are helping to change this. This is a call to action for MWs and their organisations to examine social responsibility and how they can contribute to the United Nations Resolution.[7]

Lastly, don't underestimate the value MWs

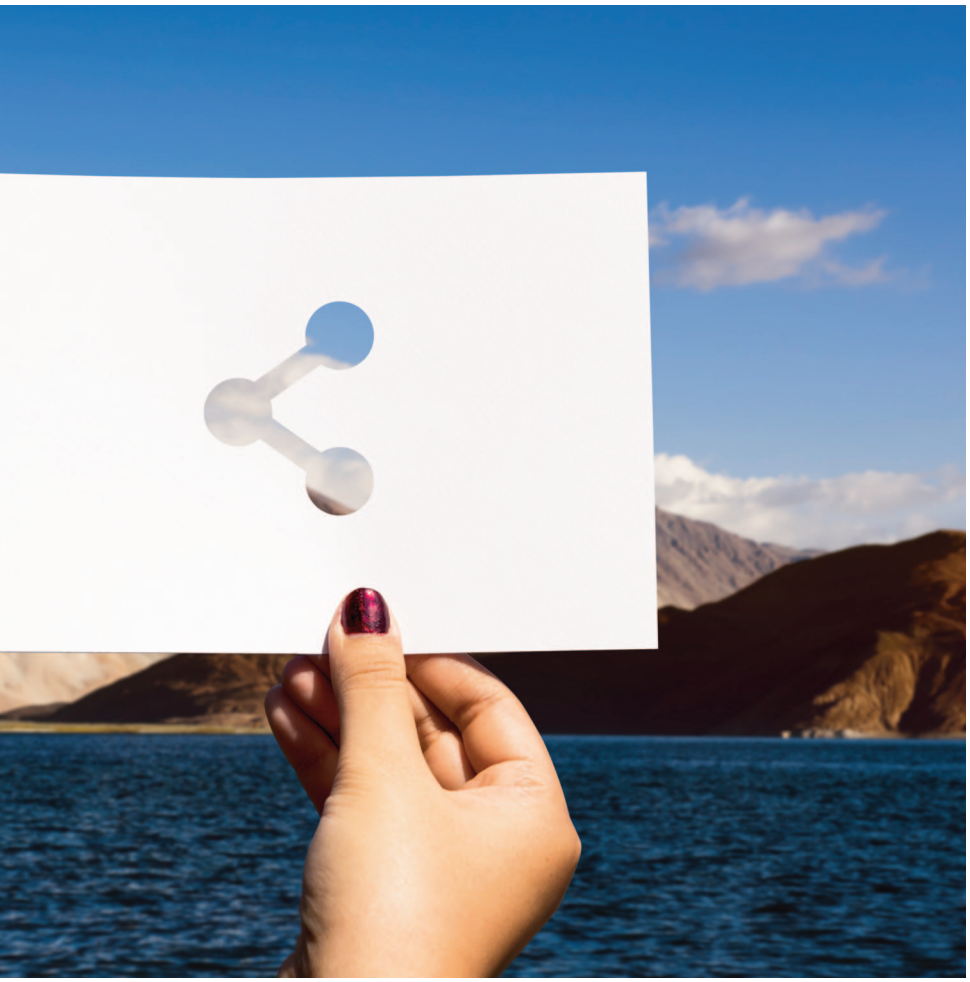

Photo: freepik

bring from their own connections and interactions with charitable organisations. Rare disease MWs tend to become proud advocates for our patients and can unlock unexpected pathways. Due to complex logistical pathways and infrastructure challenges, we have been struggling to fund appropriate measures to collect high-quality samples for our Africa Roadmap project. One of the project's MWs, who has over 20 years of experience in this field, shared with me that she attended a conference where she met with a charity interested in remote sample collection. She challenged them on whether they are considering working on this with LMICs. This led to an introduction where I learnt a lot more about the benefits of remote sample collection and all the tools that have been developed.[8] This quickly led to multiple additional introductions, with a project now planned for completion in early 2025, which is a potential game changer. This was just another example of the influence of rare disease MWs who are part of the winning team.

On multiple levels, medical writing and rare diseases are undervalued, but in LMICs they are truly forgotten. However, this can only change if we all feel our social responsibility to help those less fortunate than ourselves. Medical writing for rare diseases is a "Marmite" option, as it is frequently described; you either hate it or love it so much that it becomes part of your everyday life. Please consider joining Team Marmite. First, start by reading public social media posts on rare disease initiatives. Once you become interested and start engaging with the content, take on the challenge when a rare disease project arises. The rare disease community is wonderfully supportive and understands that everyone starts with no knowledge. Alternatively, attend rare disease sessions at conferences. Engage in conversations with attendees, and you'll quickly find yourself in meaningful discussions that may shift your work focus and definitely change your life.

On multiple levels, medical writing and rare diseases are undervalued, but in LMICs they are truly forgotten.

Disclaimers

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

Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. Bruce IA, Ezgu FS, Kampmann C, et al. Addressing the need for patientfriendly medical communications: adaptation of the 2019 recommendations for the management of MPS VI and MPS IVA. Orphanet J Rare Dis. 2022;17:91. doi:10.1186/s13023-022-02219-7
2. Taruscio D, Gahl WA. Rare diseases: challenges and opportunities for research and public health. Nat Rev Dis Primers. 2024;10(1):13. doi:10.1038/s41572-024-00505-1
3. Schrover R, Evans K, Giugliani R, et al. Minimal clinically important difference for the 6-min walk test: literature review and application to Morquio A syndrome. Orphanet J Rare Dis. 2017;12(1):78. doi:10.1186/s13023-017-0633-1
4. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2024 [cited 2024 Dec 12]. Available from: https://icmje.org/recommendations/.
5. Mease C, Miller KL, Fermaglich LJ, et al. Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: designations, diseases, and drug development. Orphanet J Rare Dis. 2024;19(1):86. doi:10.1186/s13023-024-03097-x
6. Hendriksz C, Aleksovska V, Derksen M, et al. No patient should be left behind: Pilot project to expand lysosomal disorder diagnostics in Africa. Mol Genet Metab. 2024;141(2):107879. doi:10.1016/j.ymgme.2023.107879
7. United Nations. Addressing the challenges of persons living with a rare disease and their families : resolution/adopted by the General Assembly. 2021 [cited 2025 Jan 04]. Available from: https://digitallibrary.un.org/record/3953832
8. Poland DC, Cobbaert CM. Blood self-sampling devices: innovation, interpretation and implementation in total lab automation. Clin Chem Lab Med. 2024;63:3-13. doi:10.1515/cclm-2024-0508

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An interview with Research Policy and Initiatives Director Roseline Favresse at the European Organisation for Rare Diseases

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Abstract

Roseline Favresse is the Research Policy and Initiatives Director at the European Organisation for Rare Diseases (EURORDIS). We interviewed Roseline to learn more about the rare disease landscape within Europe and the exciting recent collaborations to push research and innovation for rare diseases forward into 2025 and beyond.

Roseline Favresse is the Research Policy and Initiatives Director at European Organisation for Rare Diseases (EURORDIS). She has extensive experience in supporting the rare disease community across Europe and has been instrumental in coordinating research projects and programmes to improve rare disease education and training. This includes the development of an online open academic course entitled "Diagnosing Rare Diseases: from the Clinic to Research and Back" to train people interested in diagnostic research and rare diseases. Roseline has specialised in setting up, developing, and managing capacity-building programmes in Europe and internationally. We are honoured to have had the opportunity to interview Roseline about the rare disease landscape in Europe and about exciting recent collaborations to advance research and innovation in rare diseases.

***Medical Writing* (MW):** For our readers unfamiliar with EURORDIS, could you please describe who you are, what you do, and your mission?

Roseline Favresse (RF): EURORDIS represents over 1000 rare disease patient organisations in 74 countries across Europe and beyond, with the goal of improving the lives of the roughly 30 million people living with a rare disease.[1] We bring together stakeholders, such as clinicians, researchers, patients, families, funders, and policymakers, to allow patient voices to be heard and to help shape policy. Our mission is to work across borders and all rare diseases, including rare cancers, to improve all aspects of patients' lives. We have a three-fold strategy: advocating for people with rare diseases by working with the EU Commission and the EU Parliament; providing people with rare diseases with the tools to self-advocate through training and mentoring programmes; and also partnering them with relevant stakeholders. Our work aims to empower patients and their families so that they are recognised as equal citizens with equal rights and to ensure that people with rare diseases receive timely diagnoses.

> Early diagnosis can be improved through newborn screening programmes.

MW: What are the most significant challenges/needs reported to you from families with rare diseases?

RF: The biggest challenge is the time it takes to obtain a diagnosis. A recent retrospective patient survey using Rare Barometer, a survey initiative of EURORDIS, collected the experiences and opinions of 10,453 people living with rare diseases and their close family members in 42 European countries.[2] The survey found that it takes, on average, 5 years to diagnose a rare disease. Other key findings were that 60% of patients were misdiagnosed with a physical condition, 60% were misdiagnosed with a psychological condition, 40% had not been referred to a specialist centre, and 25% had eight or more consultations with a healthcare professional before obtaining a diagnosis (Figure 1).[3] Women have a longer diagnosis journey than men (5.4 years vs. 3.7 years). Also, children and adolescents have a longer diagnosis journey, 8.8 years and 10.4 years, respectively, which may be because symptoms are attributed to the onset of puberty. Improvements must be made in appropriate and consistent coding of symptoms and data collection to advance research.

MW: Do these challenges differ across Europe?

RF: Early diagnosis can also be improved through newborn screening programmes, and 95% of respondents in a Rare Barometer survey were in favour of performing tests to diagnose a rare disease at birth.[4,5] While widely accepted across Europe, there remain discrepancies in the availability and number of conditions included in the screening tests.[6] Certain countries do not have a newborn screening programme, while Italy has the most comprehensive screening with 48 conditions.[7] Many ongoing pilot research programmes aim at improving these newborn screening programmes at the international and local levels.

MW: The European Economic and Social Committee has called for a European flagship initiative for health and to publish an Action Plan on rare diseases with achievable targets by 2023. Has Brexit affected the inclusion of the UK in these plans? If so, how?

RF: From a EURORDIS perspective, we still work with UK groups as before. However, there has been a direct impact on the five or six European reference networks coordinated from the UK, which have a wealth of clinical

Roseline Favresse

experience. Some of the coordinators from reference networks have relocated to countries within the EU. While they can still collaborate with EURORDIS, the UK centres are no longer assured partners of the European network, which is not ideal. The situation for research is not as bad as anticipated. After some anxious months and negotiations, the UK remains associated with Horizon Europe,[8] the EU's funding programme for research and innovation.

MW: The European Rare Diseases Research Alliance (ERDERA) was launched in September 2024 to address research and funding gaps in rare diseases. Could you briefly explain its origins, mission, and key goals?

RF: ERDERA is an alliance between the European Union and member states, with around 180 partners from 37 European countries and beyond.[9] This is a 7-year initiative, with a budget of €380 million funded by Horizon Europe, member states, and public and private partners. It is the largest co-funded partnership for rare diseases in research and innovation.

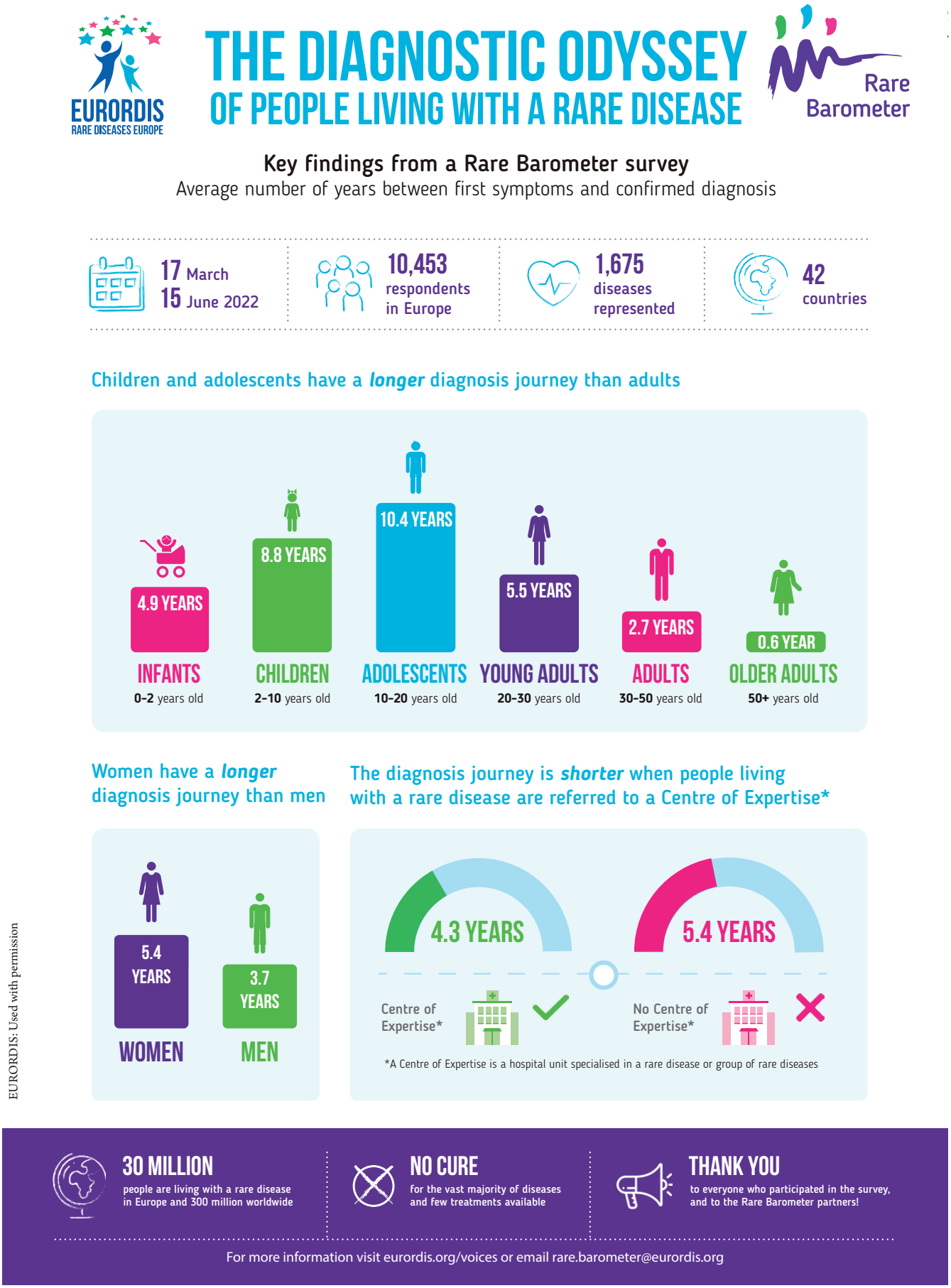
The objective is to support patient-driven research aligning with International Rare Disease Research Consortium (IRDiRC), established by the European Commission and the US NIH in 2011. The ultimate aims are to reduce the time to diagnosis to 6 months once patients have seen a medical specialist; have 1000 new therapies approved to offer treatment to the currently 95% rare diseases with no therapeutic option available; and improve evaluation and understanding of the impact of rare diseases on patients, families, and health care systems to inform policy decisions.

> The European Rare Diseases Research Alliance was launched in September 2024 to address research and funding gaps in rare diseases.

There are 25 packages with activities ranging from funding research into rare diseases to improving education and data collection, integration, analysis, and sharing at a global scale. ERDERA will develop training programmes for patients and young researchers and establish a Master's degree in rare diseases. At the moment, rare diseases are missing from the medical school curriculum in many countries, and there is a need to educate the next generation of physicians, paediatricians, and primary care practitioners.

There are services provided to the rare disease ecosystem with the goal of accelerating the translation of research into clinical development, diagnostics, and treatments. The clinical research network activities will coordinate the regulatory, outcome assessments, and data aspects in preparation for clinical trials.

There is a subcomponent in ERDERA to support national mirror groups, focusing on local issues, as well as countries currently under-represented in Horizon Europe (e.g. Portugal, Lithuania, Croatia) to ensure



EURORDIS: Used with permission

The Diagnostic Odyssey of People Living with a Rare Disease

equity of research development and access to services for rare diseases.

MW: What do you predict will be the most exciting news in 2025 for the rare disease community?

RF: We have been advocating for an EU Action Plan for rare diseases for many years, which is gaining momentum and is being endorsed by members of the EU Parliament. Also, internationally, Rare Diseases International has launched a campaign for a World Health Assembly Resolution on Rare Diseases in 2025.[10] Gaining a commitment from the WHO will improve awareness activities at a country level, setting clear targets and deadlines regarding improving diagnosis, access to care and treatment, and research development.

MW: For medical writers working in the rare disease field, what is the one quality or piece of knowledge you would like them to have to support the rare disease community in their work?

RF: Rare diseases are diverse; an individual's needs will differ from one condition to another in terms of severity and prognosis. Medical writers need the quality of empathy. For all the positive stories of advocacy we hear about, we should also look at what is behind their stories. It is essential to communicate about the ordinary and not the extraordinary. Even positive experiences will not have been without significant challenges. Also, bear in mind that not everyone has the capacity to do advocacy, which may be due to their disease, their motivation, or a variety of personal reasons. We should recognise that a lot of people with a rare disease struggle with their quality of life. For some, it is impossible to embark on researching a cure for their condition, especially as they often do not have a clear diagnosis. Living with a rare disease can be overwhelming for the average family, as not everybody relates to their daily living challenges. Individuals are frequently alienated by the healthcare environment, where their needs have been persistently overlooked. A lot has changed in a decade, though, with regard to advocacy and awareness.

Acknowledgements

EMWA sincerely thanks Roseline Favresse for taking her valuable time to participate in this interview.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. We empower, partner, and advocate for people living with a rare disease in Europe: Rare Diseases Europe-EURORDIS; 2024. Available from: https://www.eurordis.org/
2. Faye F, Crocione C, Anido de Peña R, et al. Time to diagnosis and determinants of diagnostic delays of people living with a rare disease: results of a Rare Barometer retrospective patient survey. Eur J Hum Genet. 2024:32(9);1116–26. doi:10.1038/s41431-024-01604-z
3. EURORDIS RDE. The diagnostic odyssey of people living with a rare disease. 2024. Available from: https://www.eurordis.org/wp-content/uploads/2024/05/Diagnosis-printer-.pdf.
4. EURORDIS- Rare Diseases Europe. Screening rare diseases at birth: key findings from a Rare Barometer survey on the opinion of people living with a rare disease on newborn screening 2024. Available from: https://www.eurordis.org/wp-content/uploads/2024/05/RB-FactSheet-NBS-v4.pdf.
5. EURORDIS RDE. The future of rare diseases: Leaving no one behind: Key findings from a survey on the opinion of people living with a rare disease on policies that may impact their lives. 2021. Available from: https://download2.eurordis.org/rbv/rare2030survey/factsheet/RB%20FactSheet%20Rare%202030_EN_Europe.pdf.
6. Dubief J, Gross ES, Faye F. Voices on newborn screening: the opinion of people living with a rare disease. A Rare Barometer survey with the Screen4Care project. EURORDIS-Rare Diseases Europe; 2024. doi:10.70790/NLMC2114
7. Loeber JG, Platis D, Zetterström RH, et al. Neonatal screening in Europe revisited: an ISNS perspective on the current state and developments since 2010. Int J Neonatal Screen. 2021;7(1): 15. doi:10.3390/ijns7010015
8. Horizon Europe. European Commission. Available from: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en.
9. EURORDIS. ERDERA 101: Europe's new chapter in rare disease research. 2024. Available from: https://www.eurordis.org/erdera-101-explainer/
10. Rare Disease International. World Health Assembly Resolution on Rare Diseases. 2024. Available from: https://www.rarediseasesinternational.org/wha-resolution/.

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Heather L. Mason has 14 years of freelance expertise across diverse therapeutic areas. Her passion for rare diseases emerged from professional experience and personal insight, driving her commitment to patient advocacy and inclusive healthcare communications. She is dedicated to translating complex medical information into accessible content that serves the scientific community and patient populations.

News from the EMA

The articles included in this section are a selection from the European Medicines Agency (EMA)'s News and Press Releases archive.
More information can be found on the Agency's website: www.ema.europa.eu.

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A common EU approach to data transparency in medicine regulation

December 18, 2024

EMA and HMA (Heads of Medicines Agencies) have published a comprehensive overhaul of their guidance on the identification of commercially confidential information (CCI) and personal data in marketing authorisation applications for human medicines.[1]

With the adoption of the initial guidance in 2012, European regulatory authorities agreed for the first time a common and consistent approach to identifying which parts of an application dossier can or cannot be released to the public, regardless of whether the medicine concerned has been authorised using the centralised, mutual-recognition or decentralised procedures.

As a general rule, the overwhelming majority of data in marketing authorisation applications is not considered CCI. The exceptions mainly relate to information about the manufacturing of a medicine, as well as information about facilities or equipment and some contractual arrangements between companies. While considered CCI at the time of the initial guidance, general information related to quality is now mostly considered releasable.

Instead of applying a "yes / no" rule as to whether an entire section of the dossier can be released, the updated guidance considers information as releasable by default. It provides detailed practical orientations as to which specific points could be redacted or anonymised within each section of the dossier. The annex of the guidance document has been updated and now includes examples of information that may be considered CCI or protected personal data.

The guidance also sets out how personal data will be protected if it can lead to the identification of a person. In doing so, it now considers the more recent EU legislation on data protection, namely the EU General Data Protection Regulation (GDPR) and Data Protection Regulation for the European Union institutions, bodies, offices and agencies (EUDPR). The document gives further guidance on how to identify personal data relating to experts, staff, or patients, which should be anonymised.

References

1. HMA/EMA guidance document on the identification of personal data and commercially confidential information within the structure of the marketing authorisation application (MAA) dossier. 12 December 2024. Available from: https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies-european-medicines-agency-guidance-document-identification-commercially-confidential-information-personal-data-within-structure-marketing-authorisation-application_en.pdf

New EU rules for health technology assessments become effective

January 10, 2025

EMA is ready to support the implementation of the new health technology assessment regulation (HTAR) (Regulation (EU) 2021/2282) when it becomes applicable on January 12, 2025.[1]

The regulation is an important step forward in accelerating and widening access to new medicines. In the EU, a centrally authorised medicine is accessible to patients when it has first gone through regulatory assessment by EMA and is authorised for use in patients, and secondly has been evaluated by health technology assessment (HTA) bodies to help Member States make decisions about the use, price, and reimbursement level of a new health technology taking into account its impact on the sustainability of the healthcare systems.

The regulation also creates an EU framework for the assessment of selected high-risk medical devices to help national authorities to make more timely and informed decisions on the pricing and reimbursement of such health technologies.

EMA will support the implementation of the new piece of legislation in three areas. It will:

- Support timely conduct of **joint clinical assessments (JCA)** by the HTA Coordination Group establishing relative clinical effectiveness and relative clinical safety of a new health technology as compared with new or existing technologies. In this context, EMA will provide relevant information from its own regulatory assessments
- Collaborate with the HTA Coordination Group in **parallel joint scientific consultations (JSC)** to give scientific advice to technology developers and facilitate generation of evidence that satisfies the needs of both regulators and HTA bodies
- Exchange information on upcoming applications and future health technologies, both for planning purposes and for horizon scanning.

The regulation recognises the value of cooperation between decision-makers, namely regulators who evaluate the benefits and the risks of medicines and HTA bodies who then assess their effectiveness compared to existing products. It builds on the longstanding cooperation between EMA and HTA bodies, developed with the European Network for Health Technology Assessment (EUnetHTA) until September 2023.

The new rules will initially apply to new active substances to treat cancer and to all advanced therapy medicinal products (ATMPs). They will be expanded to orphan medicinal products in January 2028, and to all centrally authorised medicinal products as of 2030. Selected high-risk medical devices will also be assessed under the HTAR as of 2026.

EMA now has a legal obligation to notify the European Commission, which serves as the secretariat to the HTA Coordination Group (HTACG), ensuring that procedures are followed and joint work is produced in a timely and transparent manner when it receives submissions for marketing authorisation applications for medicinal products in the scope of JCA. From June 2024, the Agency started identifying such applications.

References

1. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282

Human medicines in 2024

January 16, 2025

In 2024, EMA recommended 114 medicines for marketing authorisation. Of these, 46 had a new active substance which had never been authorised in the EU before. Among these are a number of medicines that stand out due to their contribution to address public health needs or the innovation they represent. The Agency recommended the first medicine to treat early Alzheimer's disease, the first needle-free and smaller form of adrenaline to treat allergic reactions, the first treatment for tumours associated with von Hippel-Lindau disease, and two new antibiotic medicines for the treatment of certain severe infections.

EMA also recommended several new vaccines, including one to protect against Chikungunya disease and a new mRNA vaccine against lower respiratory tract disease caused by respiratory syncytial virus (RSV), and extended the use of an mpox vaccine to protect adolescents from 12 to 17 years of age.

As in previous years, cancer was the strongest therapeutic area, with 28 recommendations for oncology products. There were also 28 recommendations for new biosimilar products, covering a wide range of diseases, including several types of cancer, osteoporosis, macular degeneration, and diseases that involve an abnormal immune response like plaque psoriasis, ulcerative colitis, and Crohn's disease. This is good news for patients, as biosimilars make treatments more accessible and can provide broader access to potentially life-changing medicines.

The overview of the 2024 key recommendations published today includes figures on the authorisation of medicines and a selection of new treatments that represent significant progress in their therapeutic areas.

Once a medicine is authorised by the European Commission and prescribed to patients, EMA and the EU Member States continuously monitor its quality and benefit-risk balance and take regulatory action when needed. Measures can include a change to the product information, the suspension or withdrawal of a medicine, or a recall of a limited number of batches. An overview of some of the most notable safety-related recommendations is also included in the document referenced below.

References

1. Human medicines in 2024. Available from: https://www.ema.europa.eu/en/documents/report/human-medicines-2024_en.pdf

European Shortages Monitoring Platform fully operational for monitoring of shortages in the EU

January 29 , 2025

The European Shortages Monitoring Platform (ESMP) is now live with the full scope of functionalities. This will enable marketing authorisation holders (MAHs) and national competent authorities (NCAs) to directly report information on supply, demand, and availability of nationally and centrally authorised medicines during crises and preparedness actions led by EMA's Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG).

The new release facilitates monitoring and management of critical medicines during public health emergencies and major events and in the context of preparedness activities. It follows the release of the functionalities for routine shortage reporting of centrally authorised medicines for MAHs in November 2024.

The use of the ESMP has become mandatory for MAHs and NCAs as of 2 February 2025.

The ESMP is a key requirement of EMA's extended mandate, enhancing shortages monitoring and preparedness across the EU/EEA. It gives MAHs and NCAs a platform to report accurate, complete, and timely information on the supply and demand of medicines. Harmonised reporting standards in the ESMP will lead to enhanced usability of data, and this will speed up the EU/EEA's ability to put in place coordination actions to prevent and mitigate shortages.

Publicly available information on shortages of individual medicines is accessible via the ESMP in EMA's shortages catalogue and national shortages catalogues.[1] To ensure readiness to use the ESMP, EMA invites all MAHs and NCAs to attend the webinars offered and to make use of the information material available on EMA's website.[2]

References

1. Public information on medicine shortages. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/medicine-shortages-availability-issues/public-information-medicine-shortages
2. European Shortages Monitoring Platform (ESMP), Guidance and training materials. Available from: https://www.ema.europa.eu/node/241136#guidance-and-training-materials-69020

Veterinary medicines in 2024

January 23, 2025

EMA has published an overview of its key recommendations of 2024 regarding the authorisation and safety monitoring of veterinary medicines.

In 2024, EMA recommended 25 veterinary medicines for marketing authorisation – the highest ever number of recommendations in a year. Of these, two had a new active substance which had not previously been authorised in a veterinary medicine in the EU; 14 were vaccines, including seven that had been developed by means of a biotechnological process. Among the medicines recommended for marketing authorisation in 2024, 13 were for food-producing animals, such as chickens, pigs, and cattle, and 11 were for companion animals, such as dogs and cats.

A selection of these recommendations can be found in the veterinary medicines highlights document published today.[1]

References

1. Veterinary medicines in 2024. Available from: https://www.ema.europa.eu/en/documents/report/veterinary-medicines-2024_en.pdf

Photo: Freepik

Clinical Trials Regulation becomes fully applicable

January 31, 2025

From today, all clinical trials in the European Union (EU), including ongoing trials that were approved under the previous legal framework, the Clinical Trials Directive (CTD), are governed by the Clinical Trials Regulation (CTR). This marks the end of a three-year transition period, during which more than 5,000 clinical trials were transitioned to the CTR through submission to the Clinical Trials Information System (CTIS), the single-entry point for sponsors and regulators for the submission and assessment of applications for clinical trials in the EU.

Remaining trials that are ongoing after January 30 and that were not moved to the new system may be subject to corrective measures applied by EU Member States. Transition procedures are no longer available and sponsors of ongoing CTD trials are required to submit a new application via CTIS.

CTIS includes a public searchable database for healthcare professionals, patients, and the general public to deliver the high level of transparency foreseen by the regulation. The authorisation and oversight of clinical trials is the responsibility of EU/EEA Member States while EMA is responsible for maintaining the CTIS. The European Commission oversees the implementation of the Clinical Trials Regulation. Throughout 2025, the performance and the user experience of CTIS will continue to be improved.

The full implementation of the CTR strengthens Europe as an attractive location for clinical research. The regulation streamlines the processes for the application and supervision of clinical trials, and their public registration: all clinical trial sponsors use the same system and follow the same procedures to apply for the authorisation of a clinical trial, no matter where they are located and which national competent authority (NCA) or national ethics committee they are dealing with.

Activities related to the CTR are supported by the Accelerating Clinical Trials in the EU (ACT EU) initiative,[1] a collaboration between the Heads of Medicines Agencies (HMA) in the Member States, the European Commission and EMA, which seeks to transform how clinical trials are initiated, designed and run. ACT EU features focus areas that are the basis for the ACT EU multi-annual workplan 2025-2026.[2]

References

1. Accelerating Clinical Trials in the EU (ACT EU). Available from: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/accelerating-clinical-trials-eu-act-eu
2. ACT EU multi-annual workplan 2025-2026. Version 3, December 2024. Available from: https://accelerating-clinical-trials.europa.eu/document/download/0f53c5bd-292f-4407-b891-6259f2d187aa_en?filename=ACT%20EU_workplan%202025-2026.pdf

New Chikungunya vaccine for adolescents from 12 and adults

January 31, 2025

EMA has recommended granting a marketing authorisation in the European Union (EU) for Vimkunya (applicant, Bavarian Nordic A/S), the first vaccine in the EU to protect adolescents from the age of 12 against Chikungunya. This vaccine, also intended for adults, is given as a single dose.

Chikungunya, also called CHIK fever, is a viral disease caused by Chikungunya virus (CHIKV), a virus transmitted to humans by infected mosquitoes (primarily *Aedes aegypti* and *Aedes albopictus*). Most people infected with CHIKV develop symptoms within 3–7 days. The most common symptoms of acute disease are fever and joint pain. Most patients recover within a week, but some develop joint pain for several months or longer, which can be disabling, and a small proportion of patients may develop severe acute disease, which can lead to multiorgan failure.

CHIKV infections affect people mostly in the tropics and subtropics. Chikungunya is not endemic in Europe. The majority of cases in the EU concern travellers who were infected outside of mainland Europe. Spread of the *Aedes albopictus* mosquito due to climate change could lead to cases of Chikungunya in regions so far spared.

Vimkunya was supported through EMA's PRIority MEdicines (PRIME) scheme, which provides early and enhanced scientific and regulatory support to medicines that have a particular potential to address patients' unmet medical needs.

The CHMP's opinion is largely based on data from two placebo-controlled studies. Study 1 assessed the immunogenicity and safety of the vaccine in 3,258 individuals from 12 to 64 years of age, and Study 2 in 413 older adults. The immune response was evaluated in 3,355 participants (2,748 with Vimkunya and 607 with placebo). The clinical efficacy of Vimkunya was inferred from a post-vaccination CHIKV-specific neutralising antibody titre threshold selected as a surrogate marker and referred to as seroresponse. Eight days after vaccination, the difference in seroresponse rates (SRRs) between those vaccinated with Vimkunya and those with placebo in Study 1 was 46.1%. This rose to 96% at Day 15, 96.6% at Day 22 and 84% at Day 183. In Study 2, the difference in SRRs was 79.5% at Day 15, 86.2% at Day 22 and 74.4% at Day 183.

The safety profile of Vimkunya is based on pooled data from five completed clinical studies with 3,522 participants with a 6-month follow-up. The most common side effects reported were tiredness, headache, muscle pain and injection site pain.

The CHMP has requested a post-authorisation efficacy study to confirm the effectiveness of Vimkunya in preventing Chikungunya in adolescents and adults.

EMA establishes regular procedure for scientific advice on certain high-risk medical devices

February 10, 2025

EMA, in close collaboration with the European Commission, has established a standard procedure for manufacturers of certain high-risk medical devices to request scientific advice on their intended clinical development strategy and proposals for clinical investigation.

Manufacturers of class III devices and class IIb active devices intended to administer or remove medicines can now submit their request for advice via a portal and consult the medical device expert panels at different stages of the clinical development. Advice given by the medical device expert panels is a key tool to foster innovation and promote faster patient access to safer and more effective devices.

This regular scientific advice procedure follows a pilot launched in February 2023, which has helped to establish this procedure and gathered positive feedback from manufacturers and panel experts. EMA will publish a report on the pilot in the coming weeks.

There are currently no fees associated with these requests. More information on the submission process, including step-by-step instructions for applicants and monthly submission deadlines is available on EMA's website. Manufacturers of high-risk medical devices intended for the treatment of a rare condition should apply for advice via the ongoing pilot programme to support orphan medical devices. EMA provides the secretariat to support the expert panels, based on Regulation (EU) 2022/123

Medical Devices

SECTION EDITOR

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Medical devices can be orphans, too

Raquel Billiones
Alexion, Astra Zeneca Rare Disease

doi: 10.56012/beyk2425

Definitions

Whereas the definition of orphan drugs is well established in current EU legislations, orphan devices are relatively unknown. Not defined in the EU MDR 2017/745, the MDCG 2024-10 finally provided last year the first EU-based definition of an orphan medical device – as one "*specifically intended to benefit patients in the treatment, diagnosis, or prevention of a disease or condition that presents in not more than 12,000 individuals in the European Union per year…*".[1]

In addition to rare indications, the paediatric population is also underserved in the field of medical devices as devices are, by default, designed for the adult population.[2] For paediatric purposes, instruments and implants may need to be customised or used off-label.[3] Industry experts therefore collectively call these products orphan and paediatric devices or OPDs.[3]

Below are some examples of OPDs

- *"Therapeutic devices such as microvascular plugs, which can be used for closure of patent ductus arteriosus in premature babies.*
- *Monitoring devices such as electroencephalogram… devices combined with artificial intelligence algorithms to detect seizure activity in neonates.*
- *Supportive devices such as exoskeletons used to assist mobilisation in patients with conditions such as spinal muscular atrophy, or Duchenne muscular dystrophy.*
- *Diagnostic devices such as genetic tests used for the diagnosis of many rare diseases."*[3]

Expert panels

In 2024, the EMA initiated a new pilot programme for expert panels to support manufacturers and notified bodies to address challenges faced by orphan medical devices (mainly high risk [Class IIb and Class III]), especially with respect to generating clinical evidence for these devices in the premarket phase. An information session was organised in September 2024,[4] followed by the release of a Q&A document.[5]

Photo: Freepik

The role of medical writers in orphan devices

To apply for expert panel consultation, an application form and a briefing document will be submitted. One of the key sections is the justification of the orphan status of the device based on the state-of-the-art (SoTA), e.g., the epidemiology of the disease or condition and insufficiency of current treatment options.

For legacy devices and devices in advance stages of development, the clinical evaluation report will need to include the rationale for the orphan designation that should be consistent with briefing document SoTA. Another component is the considerations for limited premarket clinical evidence, off-label use data, and extrapolation of these information to the orphan intended use.

For drug-device combination products, the link between the orphan medicinal product and the orphan device component has to be very clear.

In the nascent field of orphan devices, regulatory medical writers play a vital role in putting all these essential components together to support underserved "orphan" populations.

References

1. MDCG 2024-10: Clinical evaluation of orphan medical devices June 2024. Available at: https://health.ec.europa.eu/document/download/daa1fc59-9d2c-4e82-878e-d6fdf12ecd1a_en?filename=mdcg_2024-10_en.pdf
2. Guerlich K, Patro-Golab B, Dworakowski P, et al. Evidence from clinical trials on high-risk medical devices in children: a scoping review. Pediatr Res. 2024;95(3):615–24. doi:10.1038/s41390-023-02819-4
3. Melvin T, Dooms MM, Koletzko B, et al. Orphan and paediatric medical devices in Europe: recommendations to support their availability for on-label and off-label clinical indications. Expert Rev Med Devices. 2024;21(10):893–901. doi:10.1080/17434440.2024.2404257.
4. EMA. Information session on the pilot for expert panels' advice for orphan medical devices. Available from: https://www.ema.europa.eu/en/events/information-session-pilot-expert-panels-advice-orphan-medical-devices
5. EMA. Questions and answers on the information session on the pilot for expert panels' advice for orphan medical devices EMA/524472/2024. Available at: https://www.ema.europa.eu/en/documents/other/questions-answers-information-session-pilot-expert-panels-advice-orphan-medical-devices_en.pdf

Author information

Raquel Billiones, who has a PhD in Biology and is *Medical Writing*'s editor-in-chief, has been a regulatory writer for almost 20 years, covering both pharmaceuticals and medical devices. Her core competencies include clinical trials and marketing authorisation submission documents, data disclosure and protection, and project and people management. She is currently employed at Alexion (AstraZeneca Rare Disease).

AI/Automation

SECTION EDITORS

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Editorial

As medical writers, we know that managing references is more than just a task – it's an integral part of crafting accurate, well-supported documents. In today's fast-paced world, tools that enhance our ability to navigate, organise, and connect information are becoming indispensable. Enter **Research Rabbit**, a cutting-edge reference manager that goes beyond simple citation storage. Leveraging the power of AI, Research Rabbit enables the discovery of unexpected connections, expands research horizons, and mimics the experience of academic networking.

For writers in the medical and scientific fields, where staying on top of evolving literature is a challenge, Research Rabbit acts as an invaluable ally. It provides a dynamic and intuitive way to explore references, making the process faster and more insightful. Visualising relationships between papers, authors, and fields replicates the kind of discovery one might experience at a conference or during brainstorming sessions with colleagues.

In this issue, freelance medical writer Natasha Fallico dives into how Research Rabbit works and why it might become your go-to tool for reference management. Her exploration highlights its unique features, from interactive search capabilities to its ability to uncover trends and gaps in the literature.

As the Section Editor for AI/Automation, I'm thrilled to spotlight tools like Research Rabbit that embody the power of AI to transform how we work. This editorial serves as an introduction to Natasha's discussion and a nudge to consider how tools like this can enhance your research and writing practices. Happy reading,

Daniela

Exploring Research Rabbit: Your new favourite reference manager

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doi: 10.56012/wxzm3433

What is Research Rabbit?

Research Rabbit is a citation management tool with unique features that can be useful for exploring scientific literature and organising references efficiently. At its surface, the program functions primarily like other reference managers. Papers are searched for manually based on title or keyword and then added to a collection. Those collections are synced with research tool Zotero to generate a bibliography, which is great. But what, exactly, makes Research Rabbit unique?

Visualisation maps

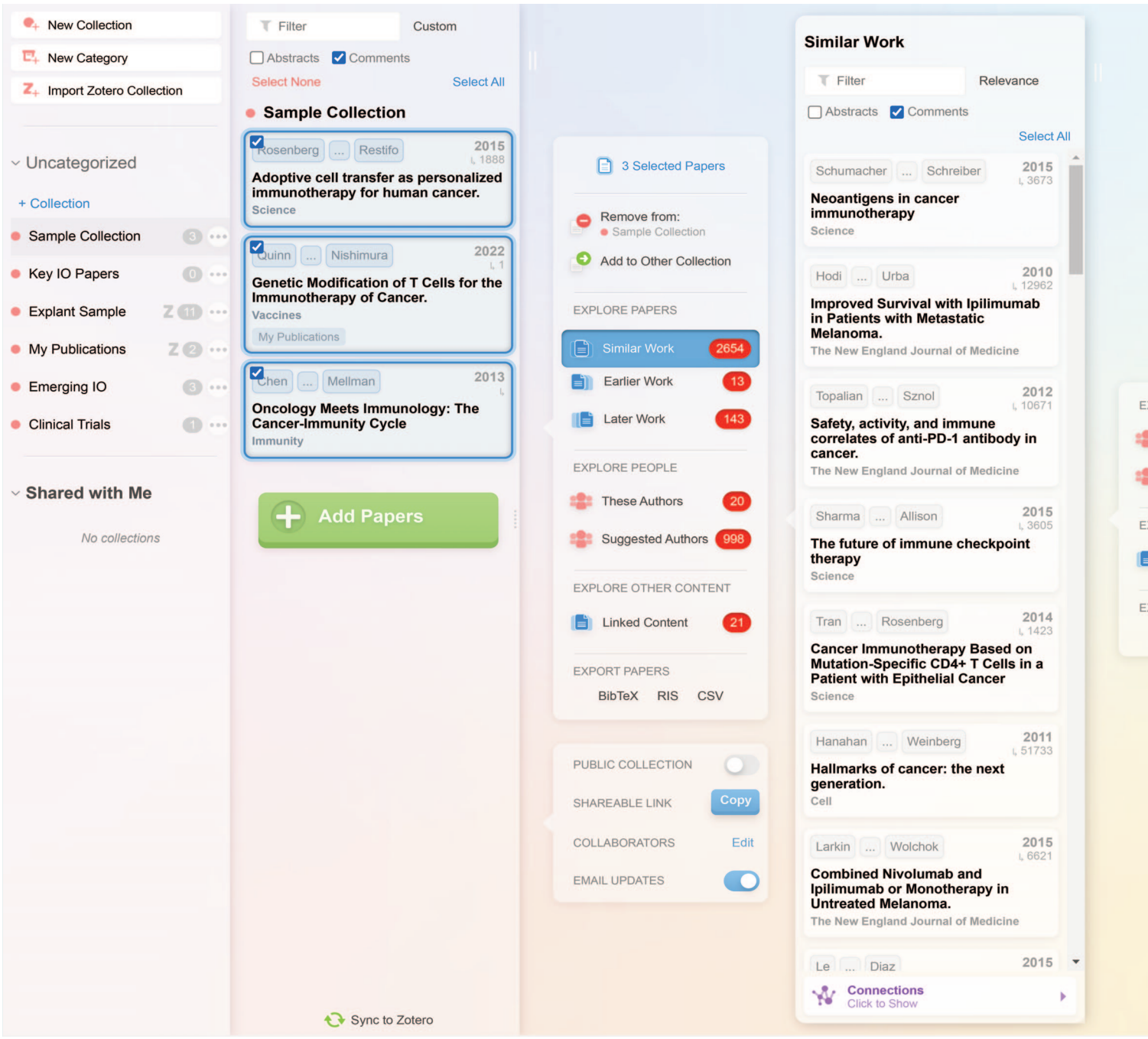
Research Rabbit's best feature is the visualisation map. After adding a paper of interest to a collection, a sidebar appears with the option to explore similar work. From there, a visualisation map appears. This map, generated by an AI-powered algorithm, recommends related articles based on the papers in that collection. Each article added to the collection, also known as a seed paper, triggers the map to update the sequence of connections. Seed papers are shown in green, and similar work will appear in blue bubbles (Figure 1). Papers within the map are selected by clicking the blue or green bubble, which will present the title, abstract, authors, and a link to the full text. If that paper is interesting, it can be immediately read or added to the collection for later review. References can be removed individually from the citation map by de-selecting them from the collection bar to zoom in on specific topics or authors. Rather than digging through entire bibliographies, writers can easily find other work by the seed authors and discover cross-referenced papers. Timeline plots organise the works by publication date to discover the most recent or earliest relevant works. The collaboration function allows users to work with other writers to generate reference collections. If a manual literature search was previously completed, but additional sources are required, references can be imported from Zotero to create a visualisation map via the 2-way syncing function. Manual literature reviews are prone to errors because they often result in an overwhelming number of open browser tabs and an overflowing downloads folder. With Research Rabbit, no papers get lost. When falling down the rabbit hole, these tools add structure to literature searches that would otherwise become tangled and confusing.

Artificial intelligence

Although many AI enthusiasts are already using this software, it is understandable that some writers may be hesitant to use AI assistance in their work. Writers often cite two concerns about using AI tools: hallucinations (manufactured, incorrect information)and losing touch with the comprehension of the work. First, hallucinations are rare because Research Rabbit is not a large language model AI, and references are sourced primarily from scholarly publications. Secondly, this tool does not use AI to summarise papers. The AI algorithm exclusively suggests similar works. It is still the writer's responsibility to read and understand the documents in their reference collection. Don't overlook Research Rabbit because AI supports it. At its core, it is simply an intelligent tool to recommend papers and encourage literature exploration.

Why you should be using Research Rabbit

The number one reason to use this tool is efficiency. Research Rabbit streamlines the process of collecting and organising references, allowing writers to spend more time focusing on reading relevant papers. Now, writers facing monstrous documents requiring hundreds of



Screenshots from researchrabbit.ai.

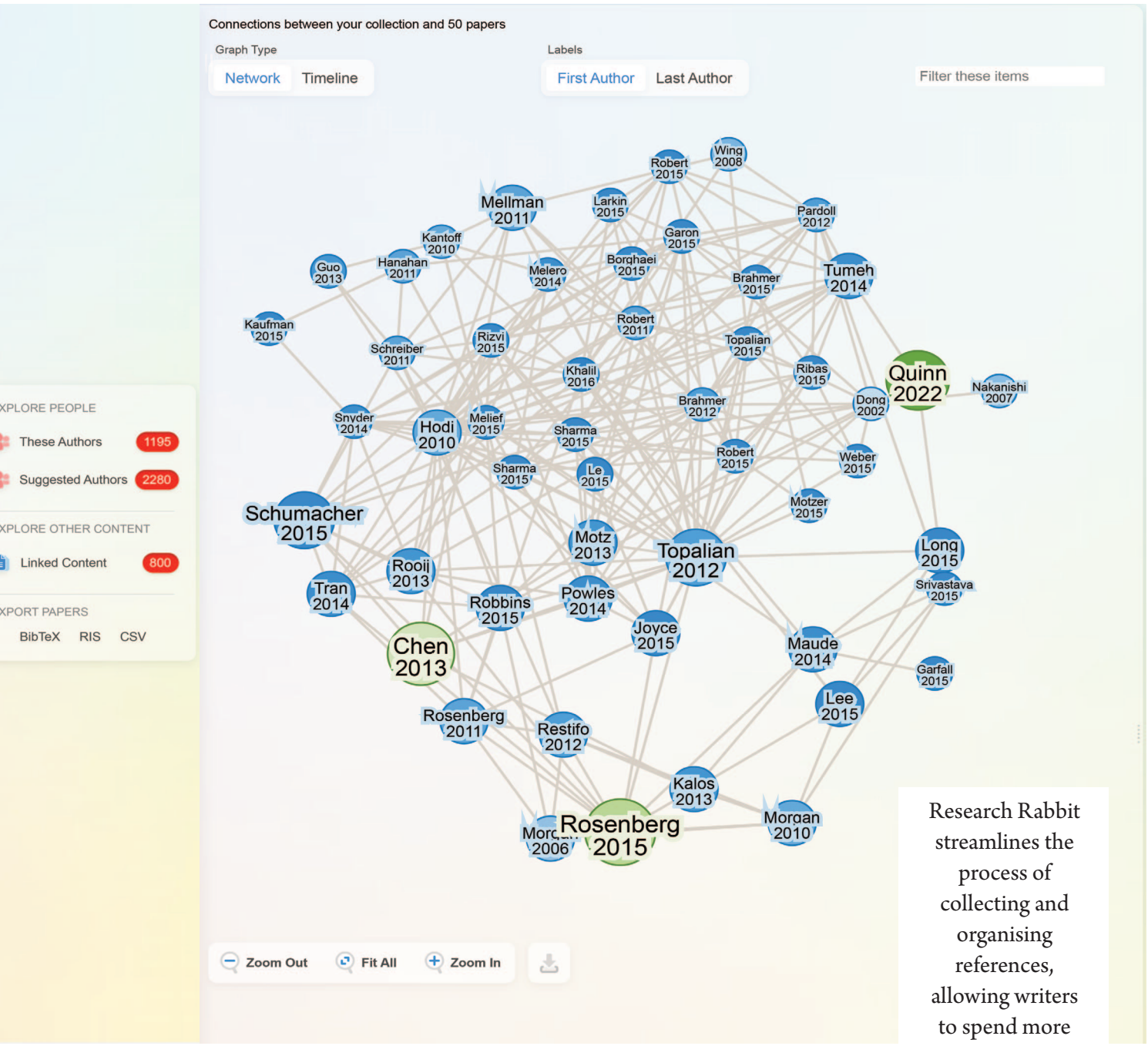
Figure 1. Example of a visualisation map based on a collection containing three papers

Seed papers are shown highlighted in blue rectangles on the left. A visualisation map generated from the seed papers including similar works is shown on the right, including a list of the works suggested within the map.

references waste less time trying to find articles and are better informed on the topic as a result. Research Rabbit will quickly deliver thousands of papers to expedite an otherwise exhaustive literature review session. However, this isn't the only literature review tool on the market. What makes Research Rabbit, in my opinion, the best?

Other literature search tools

In addition to the incredible visualisation maps, a few other features distinguish Research Rabbit from its competition. Tools like Litmaps or ConnectedPapers are popular among writers and have plenty of good features. ConnectedPapers doesn't offer Zotero integration and only accepts a single seed paper to analyze relevant articles, ultimately losing to Research Rabbit's superior functionality. Litmaps is a balanced, mature tool that comes second only to Research Rabbit. The literature analysis on Litmaps shows the top ten most relevant papers at a time. Although its suggestion prioritisation is superior and has a more user-friendly interface, Litmaps is slow. The search itself can take much longer to produce results, and viewing only ten papers at a time during a large literature review is inconvenient. While Litmaps offers many great features, Research Rabbit's reliable speed and expansive



Research Rabbit streamlines the process of collecting and organising references, allowing writers to spend more time focusing on reading relevant papers.

results make it the better option for writers. Not to mention, Research Rabbit is the only tool given here that is always free to use. In all, Research Rabbit is a fantastic resource in any writer's toolbelt. It outpaces competitors and can be seamlessly integrated into a literature search workflow to streamline the writing process.

Disclaimers

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

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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Driven by opportunities to provide better treatment options for cancer patients, Natasha helps academic institutions and pharmaceutical companies publish scientific research in immuno-oncology and bring new immunotherapy drugs to market.

Biotechnology

SECTION EDITOR

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Editorial

Vanessa Zaiatz Bittencourt wrote our very first EMWA journal Biotechnology section article in the March 2022 issue.[1] That article discussed research using animal and non-animal alternatives. In the article that Vanessa wrote for our current issue, she discusses the mental health of those who conduct research using animals then write their findings, and how their better mental health can be supported. In *Dealing with animal death and writing about it,* Vanessa highlights issues from perspectives of documentation, daily research routines, and the psychological impacts of euthanising animals. She provides some suggestions to support those using animals for research and gives her perspective on seeing colleagues involved in using animals for their research. Vanessa's article is important as while there are global efforts to reduce, replace, and refine the use of animals in research, animals are still used, and written about. And as long as research is conducted on animals, mental health support will be needed for those who euthanise animals for research purposes and then write about it.

Jen Bell

References

1. Zaiatz Bittencourt V, Chang SC. Non-animal alternatives for research and development are gaining popularity. Med Writ. 2022;31(1):111–5. Available from: https://journal.emwa.org/sustainable-communications/biotechnology/

Dealing with animal death and writing about it: Cultivating resilience in biotechnology writing

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doi: 10.56012/dgla9046

Ensuring safety through documentation and post-market testing

In the realm of medical writing, the task of documenting research findings is not merely a procedural step but a critical component of the scientific process. Writing serves as a cornerstone in ensuring successful regulatory authorisation for products to reach the market. The precision and clarity of scientific documentation are essential in demonstrating the efficacy, quality, and safety of a product to regulatory bodies.[1] Properly documented findings ensure that potential risks are identified and mitigated, safeguarding patients and building public trust in biomedical advancements. For scientists and researchers involved in *in vivo* and *in vitro* experimentation, this responsibility takes on an added layer of complexity. These individuals have a double job, they are writers and scientists or researchers. We must remember that a scientist and or a researcher is also a writer.[2]

Researchers involved with *in vivo* studies are not only tasked with the emotional burden of ending an animal's life[3] but also with the meticulous documentation of their results. This documentation spans books, scientific publications, and protocols, while also serving as a vital means of effectively communicating findings to healthcare providers and stakeholders.[1] This dual role underscores the importance of medical writing in translating complex research data into coherent, accessible information. By carefully recording the outcomes of their experiments, these researchers contribute to the broader scientific community, ensuring that their findings can be scrutinised, replicated, and built upon. This process is essential for advancing medical knowledge and developing new treatments, highlighting the indispensable role of medical writers in the research ecosystem.

The use of animals in research has been a controversial topic for decades, with supporters and opponents on both sides of the debate.[4] While animal research has been crucial in advancing scientific understanding and improving human health, the treatment of animals used in research remains a contentious issue.[5-7]

The mental health of scientists working in biotechnology, particularly those involved in

animal research, is a critical yet often overlooked area of concern. This article aims to provide a comprehensive overview of the mental health challenges faced by biotechnology scientists engaged in animal research and scientific writing, focusing on the stressors unique to this field and proposing strategies for mitigation.

A day in the life of a researcher who uses animals for work

The life of a researcher is thoroughly planned and multifaceted. It begins with outlining the day's experiments, ensuring every step is well-documented and every protocol followed precisely. Researchers organise the necessary chemicals, verifying concentrations and volumes to maintain accuracy. They schedule the use of essential equipment like real-time PCR machines, flow cytometers, and biosafety cabinets, coordinating with colleagues to avoid scheduling conflicts. For many, a visit to the animal facility is essential, where they plan and conduct experiments, carefully considering ethical guidelines for animal care and use. This includes determining the method of euthanasia, the organs to be harvested, and the subsequent techniques for analysis.

The daily life of a scientific researcher working at the bench is a blend of creativity, rigorous research, and structured routine. On top of this routine, we must remember that a researcher is also a writer. The researcher must review current scientific literature to stay updated on the latest developments and breakthroughs. This is followed by outlining and drafting articles, while developing hypotheses and thinking about future experiments. Deadlines are a constant companion as well, requiring efficient time management and the ability to quickly turn around revisions.[8,9]

Interactions with editors, researchers, and other writers is frequent. Balancing writing with research time is extremely challenging and significantly impacts a researcher's mental well-being.[2] It's no surprise that mental health in the biotechnology field is both crucial and often overlooked, as finding alternatives to change this demanding routine remains difficult. To mitigate these issues, it is crucial for employers to provide mental health resources, create supportive work environments, and encourage open discussions about mental health.

The psychological impact of animal research

Scientists involved in animal research often experience ethical dilemmas that can lead to profound moral distress.[3,10] The conflict between the pursuit of scientific knowledge and the welfare of animals creates an ethical tension that can weigh heavily on researchers.[11] The necessity of euthanising animals, performing invasive procedures, and witnessing animal suffering can lead to intense feelings of guilt, sadness, and anxiety, impacting the research and writing skills.[5] These emotional burdens, if left unaddressed, can contribute to long-term psychological stress, potentially resulting in burnout and other serious mental health issues. While there are regulations in place to ensure the welfare of research animals,[12] recent studies have highlighted the mental toll that researchers using animals face.[3,10]

While there are regulations in place to ensure the welfare of research animals, recent studies have highlighted the mental toll that researchers using animals face.

Compassion fatigue,[13] a form of secondary traumatic stress, is a significant risk for these researchers. This condition arises from the emotional distress experienced when individuals are exposed to the traumatic experiences of others, often shown in healthcare workers. In the context of animal research, scientists are repeatedly exposed to distressing situations, such as handling and caring for animals that will undergo or have undergone painful procedures. This continuous exposure can lead to emotional exhaustion, characterised by a diminished

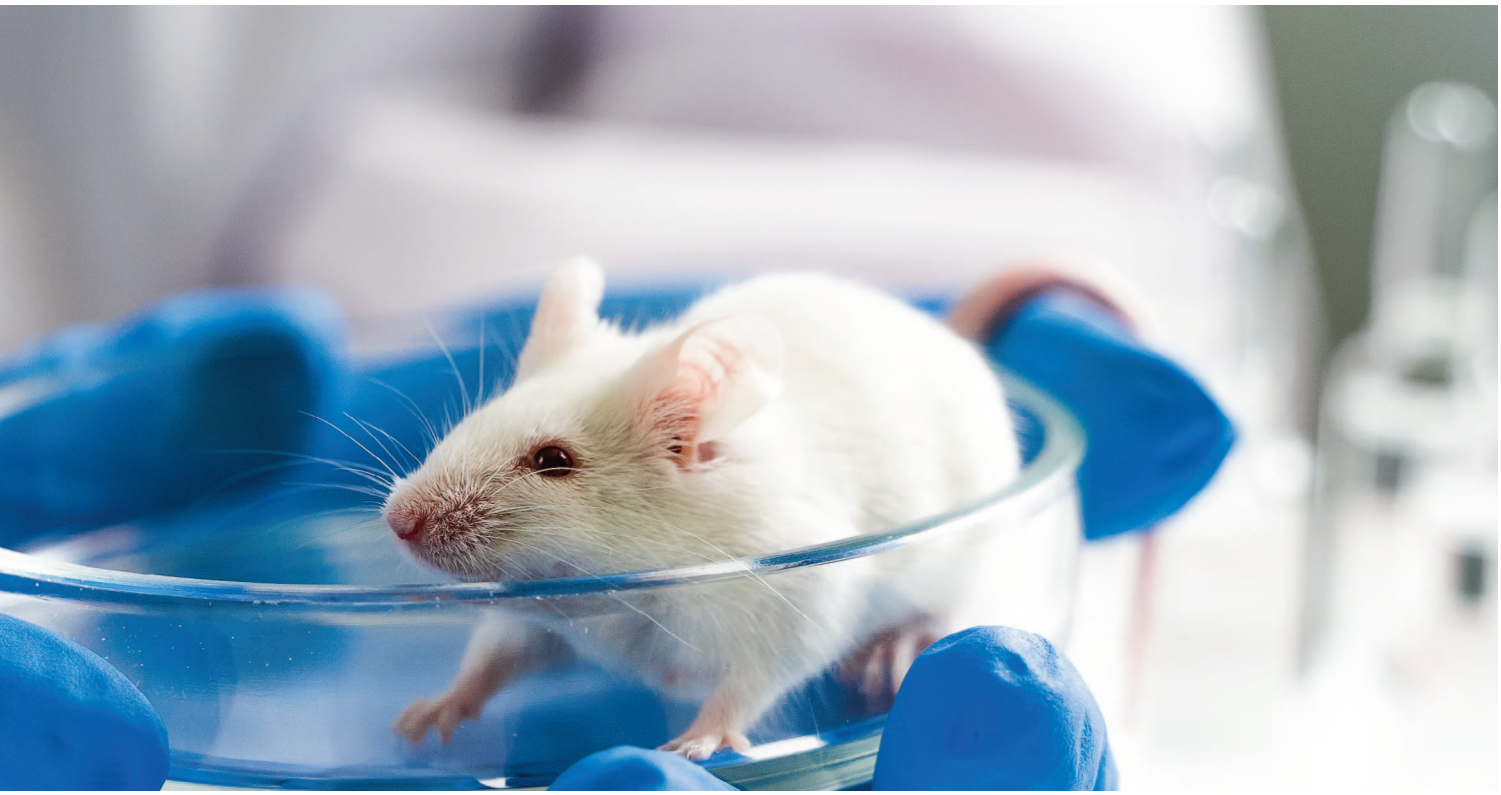

Photo: Freepik

capacity for empathy and emotional engagement. Over time, the relentless cycle of witnessing animal suffering and death can erode a researcher's emotional resilience, impacting both their personal well-being and professional performance.

The consequences of compassion fatigue are far-reaching.[13,14] Personal relationships may suffer as researchers struggle with the emotional toll of their work. Professionally, this exhaustion can lead to decreased job satisfaction, reduced productivity, and increased turnover rates.[15] Additionally, the inability to engage empathetically can affect the quality of care provided to the animals and the integrity of the research itself. Research animals that are badly handled promote animal behavioural changes and altered physiological responses, which may affect the results of experiments.[14] To mitigate the effects on human mental health, it is crucial for institutions to provide support systems, such as counselling services, peer support groups, and training in stress management and self-care techniques.[13]

Strategies for systemic change concerning animals in research

Strategies for systemic change need to consider the needs of those involved in animal research. It is important to keep in mind that all research must be written up, and many researchers transition to industry medical writing roles. Notably, industry is increasingly embracing animal research replacement, reduction and refinement (the 3Rs), driving innovation in alternative methods and influencing academic research to adopt these principles, thereby fostering a more ethical and sustainable research environment.[16,17]

Institutional support systems

To address the mental health crisis in academia, institutions must implement robust support systems.[18,19] These may include:

- Access to mental health services: Providing easily accessible counselling and mental health services for students.
- Workshops and training programmes: Offering workshops on stress management, resilience, and coping strategies.
- Mentorship programmes: Establishing mentorship programmes that promote healthy mentor-mentee relationships and provide guidance on navigating academic challenges.

Role of principal investigators (PI)

PIs play a crucial role in promoting mental well-being within their research groups.[17,20] PIs should:

- Model healthy behaviours: Demonstrate a commitment to their own well-being and encourage a healthy work-life balance.
- Foster open communication: Create an environment where students feel comfortable discussing their mental health concerns without fear of judgement or repercussions.
- Provide support and resources: Actively support students in accessing mental health resources and developing coping strategies.

Empowering trainees

Graduate students must also take an active role in managing their mental health.[21] They should:

- Be attentive to mental health: Recognise signs of mental distress and take proactive steps to address them.
- Seek professional help: Utilise available mental health services and seek professional help when needed.
- Develop coping strategies: Engage in activities that promote mental well-being, such as exercise, mindfulness, and maintaining a healthy work-life balance.

Promoting a supportive work environment

Creating a culture of openness and support within research institutions is essential. Encouraging open discussions about mental health, providing training on recognising and addressing mental health issues, and fostering a non-judgemental atmosphere can help reduce stigma and promote well-being.[20,22]

Using animal alternatives in research[6] such as novel methodologies to substitute animals, not only promotes ethical practices but also fosters a supportive work environment that can reduce the mental health issues faced by scientific researchers.[13] By implementing innovative techniques that replace or minimise the use of animals in experiments, researchers can alleviate the ethical dilemmas and emotional distress associated with animal research.[5] This shift towards alternative methods not only aligns with the 3 Rs (reduction, replacement and refinement) principles of humane treatment of animals but also contributes to a more positive workplace atmosphere.[6,11]

Improved mental well-being can enhance researchers' cognitive function, creativity, and productivity, leading to more effective problem-solving and innovative scientific discoveries.[23] In this way, promoting animal alternatives and supporting researchers' mental health go hand in hand, ensuring their findings are communicated effectively and with passion.[16]

Conclusion

The act of writing up results serves as a form of cognitive processing for researchers, allowing them to reflect on their work and its implications. By framing their experiences within the context of scientific inquiry, researchers can find meaning and purpose in their work. Additionally, the detailed documentation required in medical writing ensures that the ethical considerations and humane practices employed during the research are transparently communicated. This transparency not only upholds the integrity of the research but also fosters a culture of accountability and ethical responsibility within the scientific community. In this way, medical writing becomes a crucial step for researchers to take the reins, transforming their experiences into valuable scientific contributions. Scientists and writers engaged in animal research is a multifaceted issue that requires comprehensive attention and proactive measures. By addressing the unique stressors associated with this work and implementing supportive strategies, research institutions can foster a healthier, more resilient workforce.

There are different perspectives on this issue, but from what I've seen, most people didn't enjoy the aspect of animal research that involved euthanising mice for their studies.

Post script: A personal perspective on people involved in animal research

During my time in my master's and PhD programme, I saw how using animals in research could weigh heavily on my colleagues who had no other option. Whenever someone had to head to the animal house, you could tell from their faces that they weren't thrilled about it. Some even grumbled about wishing for alternatives that just weren't available yet, or that their PI was not interested in trying something new.

When they came back up with organs in plastic tubes, their expressions never looked happy. While there were some who didn't seem bothered at all and even went on to run labs focused solely on animal research, others decided to go a different route. After graduating, some of my colleagues vowed never to work with animals again, choosing instead to work exclusively with human samples. It's clear that there are different perspectives on this issue, but from what I've seen, most people didn't enjoy the aspect of animal research that involved euthanising mice

for their studies. It's something that I think PIs often overlook – how doing animal research affects the mental well-being and enjoyment of research for their team members

Disclaimers

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Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. Oronsky B, Burbano E, Stirn M, et al. Data Management 101 for drug developers: A peek behind the curtain. Clin Transl Sci. 2023;16(9):1497–509. doi:10.1111/cts.13582.
2. Pain E. Why World Mental Health Day matters for scientists. ScienceAdviser. 2018. Available from: https://www.science.org/content/article/why-world-mental-health-day-matters-scientists
3. Rumpel S, Kempen R, Merle R, et al. Psychological stress and strain in laboratory animal professionals - a systematic review. Lab Anim. 2023;57(4):396–411. doi:10.1177/00236772221129111.
4. Kaplan BLF, Hoberman AM, Slikker W, Jr, et al. Protecting human and animal health: the road from animal models to new approach methods. Pharmacol Rev. 2024;76(2):251–66. doi:10.1124/pharmrev.123.000967.
5. Grimm D. Suffering in silence. Science. 2023;379(6636):974–7. doi:10.1126/science.adh4770.
6. Zaiatz-Bittencourt V, Chang SC. Non-animal alternatives for research and development are gaining popularity. Med Writ. 2022;31(1):111-5.
7. Domínguez-Oliva A, Hernández-Ávalos I, Martínez-Burnes J, et al. The importance of animal models in biomedical research: current insights and applications. Animals (Basel). 2023;13(7):111–5. doi:10.3390/ani13071223
8. Friedrich J, Bareis A, Bross M, et al. "How is your thesis going?"– Ph.D. students' perspectives on mental health and stress in academia. PLoS One. 2023;18(7):e0288103. doi:10.1371/journal.pone.0288103.
9. Riley A. On being a science writer and managing a mental illness. The Open Notebook - blog. 2017 [cited 2024 Nov 28]. Available from: https://www.theopennotebook.com/2017/07/18/on-being-a-science-writer-and-managing-a-mental-illness/
10. Ahn N, Park J, Roh S. Mental stress of animal researchers and suggestions for relief. J Anim Reprod Biotechnol. 2022;37(1):13–6. doi:10.12750/JARB.37.1.13
11. Young L, Ferrara F, Kelly L, et al. Professional quality of life in animal research personnel is linked to retention & job satisfaction: A mixed-methods cross-sectional survey on compassion fatigue in the USA. PLoS One. 2024;19(4):e0298744. doi:10.1371/journal.pone.0298744.
12. DIRECTIVE 2010/63/EU on the protection of animals used for scientific purposes: European Union; 2010. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF
13. Collaborative TR. Compassion fatigue resiliency 2024 [cited 2024 Nov 28]. Available from: https://3rc.org/compassion-fatigue/.
14. Van Hooser JP, Pekow C, Nguyen HM, et al. Caring for the animal caregiver – occupational health, human-animal bond and compassion fatigue. Front Vet Sci. 2021;8;731003. doi:10.3389/fvets.2021.731003
15. Goñi-Balentziaga O, Vila S, Ortega-Saez I, et al. Professional quality of life in research involving laboratory animals. Animals. 2021;11(9):2639. doi:10.3390/ani11092639
16. Roome S. Mental Health & Wellbeing for Scientists: Support Pack. HelloBio. 2021. [cited 2024 Nov 28]. Available from: https://hellobio.com/blog/mental-health-and-wellbeing-for-scientists-support-pack.html
17. Tsouros AD, Dowding G, Thompson J, Dooris M. Health promoting universities: concept, experience and framework for action. WHO. 1998(EUR/ICP/CHVD 03 09 01) [cited 2024 Nov 28]. Available from: https://iris.who.int/handle/10665/108095
18. Watson D, Turnpenny J. Interventions, practices and institutional arrangements for supporting PGR mental health and wellbeing: reviewing effectiveness and addressing barriers. Stud High Educ. 2022;47(9):1957–79. doi:10.1080/03075079.2021.2020744
19. da Silva Souza RC, Bersaneti MD, Dos Santos Yamaguti WP, et al. Mentoring in research: development of competencies for health professionals. BMC Nurs. 2023;22(1):244. doi:10.1186/s12912-023-01411-9.
20. Smith JM, Smith J, McLuckie A, et al. Exploring mental health and well-being among university faculty members: a qualitative study. J Psychosoc Nurs Ment Health Serv. 2022;60(11):17–25. doi:10.3928/02793695-20220523-01.
21. Ganapati S, Ritchie TS. Professional development and career-preparedness experiences of STEM PhD students: gaps and avenues for improvement. PLoS One. 2021;16(12):e0260328. doi: 10.1371/journal.pone.0260328
22. Mercer J, Thomas J. How understanding doctoral researchers' coping strategies can inform higher education institutions' response to their stress. Res Post-Compulsory Educ. 2024;29(1):117–37. doi:10.1080/13596748.2023.2285632.
23. Bernstein R. The health of those who study health. Science. 2015;348(6242):1506. doi:10.1126/science.348.6242.1506

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https://scholar.google.com/citations?user=AhPjFhoAAAAJ&hl=en

My First Medical Writing

SECTION EDITOR

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Editorial

After a short break, this section is back to highlight the work of new and aspiring medical writers. For this issue, I had the pleasure of working with Micko Calizon on his article about the role of AI in HIV detection and AIDS prevention. Micko is an aspiring medical writer with a Master's in Biomedical Sciences from the University of the West of England. Throughout his academic journey, he enjoyed translating scientific data and literature into digestible content, from conference posters to journal manuscripts. Since graduation, he has explored different career opportunities within medical communications to develop his writing and comprehension skills. He is now excited to find his niche within the industry and this article is one of his first key milestones. I hope you enjoy this read! **Evguenia**

Could AI play a key role in the fight against HIV/AIDS?

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doi: 10.56012/avjy7101

Since its discovery in 1983, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) has been a recognised global public health issue. However, what was once considered an incurable disease is becoming increasingly treatable and manageable. Interventions for HIV/AIDS such as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) have been developed to minimise the risk of HIV transmission before and following sexual intercourse. Additionally, antiretroviral therapies (ARTs) suppress viral replication within cells, lessening viral load and improving the quality of life for HIV patients.[1] Novel technologies such as artificial intelligence (AI) and machine learning (ML) have shown promise in aiding initiatives aimed at HIV prevention and management. Could AI be the next key player in the fight against HIV/AIDS?

> These models significantly accelerated distribution calculations of supply chains within Kenya and Tanzania, reducing the time taken to generate medication forecasts from 3 days to 15 minutes and 3 weeks to 1 day, respectively.

HIV screening and diagnosis

AI has been used to identify individuals at risk of HIV in countries like Ukraine, which has one of the highest increases in HIV/AIDS cases outside of Africa.[2] Following the declaration of the Russia-Ukraine war, fears of an increase in HIV cases arose due to potential disruptions in case finding and accessible healthcare. To combat this potential risk, The Alliance for Public Health, an HIV advocacy organisation within Ukraine, used ML algorithms to increase HIV screening. For example, they utilised a ML model that used data from screening questionnaires to identify people at risk of HIV within an HIV-positive person's network. The model demonstrated a 37% better ability in HIV case detection than non-ML methods, with a recorded 5.2% HIV detection rate.[3] Data from this study was used by the government to successfully recruit individuals believed to be at risk of contracting HIV.

A similar model was used in Kenya and Uganda where ML methods identified candidates at risk of contracting HIV. The Sustainable East Africa Research in Community Health (SEARCH) study is a research programme investigating the impact of early HIV diagnosis and ART treatment on rural communities in East Africa. Researchers within the study used data from 16

Photo: Freepik

Photo: Freepik

communities within Uganda and Kenya to create an algorithm-generated risk score that identified high-risk individuals. ML was more sensitive than other methods, correctly identifying 78% of seroconversions (where the body starts producing detectable levels of HIV antibodies) compared to 58% with risk-group strategies and 68% with a model-based strategy. ML methods were also more efficient, targeting 18% of the population while the risk-group strategy targeted 42% and the model-based strategy targeted 27% of the population to achieve the same result.[4]

Roles surrounding treatment

In Africa, AI algorithms have been used to accelerate the distribution process of essential medications managed by supply chains. In Kenya and Tanzania, traditional methods of predicting treatment demands are typically time-consuming and at risk of inaccuracies. An East African health firm called inSupply Health integrated predictive ML models into supply chain systems to improve the accuracy of forecasting the need for medications. These models significantly accelerated distribution calculations of supply chains within Kenya and Tanzania, reducing the time taken to generate medication forecasts from 3 days to 15 minutes and 3 weeks to 1 day, respectively.[5] These methods could be applied to the management of HIV medications such as ARTs or PrEP to streamline their distribution.

Different ML algorithms can be used to predict the likelihood of events. Logistic regression algorithms estimate the probability of a binary result, such as a "positive" or "negative".[6] One such algorithm was used to create predictive tools to detect viral nonsuppression in HIV-positive people who received at least one year of HIV care. This tool was successful in identifying variables that predicted the outcome of HIV treatment and can be used to triage those requiring more intensive care. The model was also found to possess good discriminative performance to distinguish between classified groups.[7]

> However, it is important to remember that AI is not faultless and should not replace human-led techniques.

Limitations of AI

AI is a promising tool for improving HIV diagnostic regimens and speeding up processing operations, but there are still some challenges to face before AI models can be widely implemented. Studies on AI techniques are still in their infancy with many studies only focusing on AI in HIV prevention and treatment and less on topics such as finding a cure. Most of these studies also use more basic or conventional ML models rather than recent, more advanced ones. A potential reason for this is the multidisciplinary approach that typically involves researchers within HIV, health professionals, and programmers.[8] The more advanced AI algorithms need to be customised to particular problems or populations which can be time-consuming, costly, and requires optimisation.

Furthermore, there are still concerns surrounding the privacy, security, and ownership of data used by AI as the algorithms generally require large amounts of data to operate. It may not always be possible to trace the source of data to determine if it was obtained ethically or not, especially when using extensive datasets.

Ensuring the data was obtained legally and with permission from participants is crucial when handling sensitive data such as a patient's HIV status. Also, the potential for bias exists (particularly if data from a particular group is limited) as algorithms learn from a given dataset and may not be able to detect any biases within the data. As a result, certain demographics may be underrepresented, for example, and results may not be fair, questioning the reliability of data.[9]

The future of AI research

AI and ML show great promise in advancing current research around HIV prevention and treatment. Machine-led techniques can significantly reduce processing times, reduce the possibility of human error, and correctly identify certain characteristics or variables within data. However, it is important to remember that AI is not faultless and should not replace human-led techniques. Instead, it seems AI is best used in conjunction with human supervision to aid current research rather than relying solely on it. As AI's role within science continues to be explored, there could be many uncovered possibilities. Studies have yet to use AI in finding a cure for HIV, which would take us one step closer to eradicating HIV/AIDS.

References

1. Akudibillah G, Pandey A, Medlock J. Maximizing the benefits of ART and PrEP in resource-limited settings. Epidemiol Infect. 2017;145(5):942–56. doi:10.1017/S0950268816002958.
2. Colborne M. Ukrainians battle escalating HIV epidemic. CMAJ. 2017;189(26): E901–2. doi:10.1503/cmaj.1095410
3. Holt E. AI-assisted HIV case finding in Ukraine. Lancet Microbe. 2024;5(7):631. doi:10.1016/S2666-5247(24)00077-6
4. Balzer LB, Havlir DV, Kamya MR, et al. Machine learning to identify persons at high-risk of human immunodeficiency virus acquisition in rural Kenya and Uganda. Clin Infect Dis. 2020;71(9):2326–33. doi:10.1093/cid/ciz1096
5. Impact stories – inSupplyHealth. 2022 [cited 2024 Nov 25]. Available from: https://insupplyhealth.com/impact-stories/
6. Maalouf M. Logistic regression in data analysis: an overview. Int J Data Anal Tech. 2011;3(3):281. doi:10.1504/IJDATS.2011.041335.
7. Gebrezgi MT, Fennie KP, Sheehan DM, et al. Development and validation of a risk prediction tool to identify people with HIV infection likely not to achieve viral suppression. AIDS Patient Care STDs. 2020;34(4):157–65. doi:10.1089/apc.2019.0224
8. Xiang Y, Du J, Fujimoto K, et al. Application of artificial intelligence and machine learning for HIV prevention interventions. Lancet HIV. 2022;9(1): e54–62 [cited 2024 Dec 2]. doi:10.1016/S2352-3018(21)00247-2
9. Ferrara E. Fairness and bias in artificial intelligence: a brief survey of sources, impacts, and mitigation strategies. Sci. 2023;6(1):3. doi:10.3390/sci6010003

Good Writing Practice

Distractions in the introduction section of a journal article

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Introduction

The Introduction section of a journal article can be distracting when expressing or not expressing the conceptual components. For example, background to the research problem if peripheral rather than pertinent would detract from a focus on the argument. The Research problem would be distracting by dogmatically stating an absence of a published article. Another distraction would be the omission of a hypothesis, which was undoubtedly centerfold in the grant supporting the research. Lastly, not including the objective and the experimental approach would eliminate the segue to the methods section.

Verb tense is an important component of writing with clarity and focus.

1. Present tense

*Protein A **is** larger than protein B (Smith, 1990)*

Use of the present tense is thematically focused and accepted by the current author and/or the discipline as being valid; a timeless truth.

2. Past + present tense (hybrid)

Example 1

*Smith (1990) **confirmed** that protein A is larger than protein B.*

This example has the same meaning as in Point 1 but the emphasis is on the previous investigator; the current author and discipline accept the statement.

Example 2

*Smith **reported** (Ref.) that protein A is larger than protein B.*

*It **was reported** by Smith (Ref.) that protein A is larger than protein B.*

***According to Smith** (Ref.) protein A is larger than protein B.*

In these examples, the statements are solely the responsibility of the previous investigator.

3. Past + past tense

*Smith **reported** (Ref.) that protein A **was** larger than protein B.*

Acceptance of the statement is solely the responsibility of the previous investigator. This example is essentially the same as the past + present tense (hybrid) examples but the inference is that the current investigator is less accepting of the statement.

4. Present perfect + present tense (hybrid)

*Smith **has reported** (Smith, 1960) that protein A is larger than protein B.*

The inference in this format is that the current author and/or the discipline accept the statement. An effort to convey "recently" is grammatically incorrect because the time is fixed to the past (e.g., 1960).

Conclusion

The Introduction section of a journal article should be focussed and relevant. The tense in which the text is written can make a subtle difference to the meaning.

Freelancing

SECTION EDITOR

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Editorial

The Freelance Business Forum is a staple of every EMWA conference, an informal networking event for freelancers or anyone interested in freelancing. This event is organised by the Freelance Business Group, whose members present its mission and activities. Afterwards, there is a presentation by a guest speaker or, as done at the May, 2024 conference in Valencia, Spain, a panel discussion with experts answering audience questions. The session then moves towards roundtable discussions, where each table moderator guides the conversation on a specific topic. This setup works well whether in person or online, allowing attendees to easily switch between topics. At the end of the discussions, each moderator shares a quick summary so everyone can learn from their group conversations.

It is a highly interactive session and one of my personal favourites at EMWA conferences. Here, I provide a report of the Forum at the Virtual Conference held in November 2024.

Happy reading, and consider joining us at the next forum at the Riga, Latvia, conference in May 2025!

Adriana Rocha

Report on the Freelance Business Forum at EMWA's 58th Conference (Virtual) in November 2024

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doi: 10.56012/klbn4782

Freelance Business Forum

The virtual Freelance Business Forum (FBF) had 40 attendees and was hosted by Adriana Rocha, Chair of the Freelance Business Group (FBG), who presented the group and its activities. The Group consists of five members: Adriana, Beate Walter, Johanna Chester, Heather Mason, and Jessica Norberg (who joined the group after the conference). The main goal of the FBG is to support EMWA's freelancers.

Previous FBG activities include the 2023 *Medical Writing* special journal issue on Freelancing, found at https://journal.emwa.org/freelancing. There is also the dedicated LinkedIn group where freelancers can connect, share experiences, and seek advice, the EMWA Freelance Business Forum – Online LinkedIn group, at https://www.linkedin.com/groups/12769131/.

Speaking of the *Medical Writing* journal, the *Freelancing* section has replaced the former *Out On Our Own* section, with Adriana as the new section editor. Freelancers are welcome to share their article ideas by reaching out to freelance@emwa.org. The newly-renamed section was inaugurated in June 2024 with an article by Laura Kehoe, who shared her experiences during her 6-year tenure as the previous Chair of the FBG. It is definitely worth a read: https://journal.emwa.org/soft-skills-for-medical-writers/freelancing/

Looking at future activities, the Freelance section of the EMWA website is being updated, alongside the larger EMWA website redesign, which may take some time to complete. One service hosted on the website is the Freelance Directory, a paid service for freelancers. An informal poll during the event revealed that only half of the attendees (57%) were signed up for the directory, but that the majority (85%) would join it if it were improved. The FBG is aware of this issue and is studying how best to improve it.

> Of hybrid work, one attendee likened it to employment being the cake and freelancing being the icing.

Additionally, following the 2023 Freelance Business Survey, there will be a 2025 survey, now led by the larger Remuneration and Salary Compensation Team (which includes FBG members). The survey will collect remuneration data from all medical writers: freelance, hybrid, and full-time employees. The survey is expected to launch in 2025 and the results will be published in *Medical Writing* in 2026.

The FBF continued with a presentation by the guest speaker, Eleanor Steele. Eleanor has worked in MedComms since 2004, first as a medical writer and then as team leader in several different agencies. She is currently a freelance consultant working as the MedComms Mentor and since April 2024 also manages the MedComms Workbook, a subscription service for MedComms freelancers.

Eleanor spoke about taking control of your freelance career. While freelancing can be a fantastic way to build a career you love, there are many challenges. She emphasised the importance of understanding your individual career goals and setting boundaries to help you choose projects with intention and work in a sustainable way.

Eleanor noted that it can be hard to find professional development opportunities as a freelancer, but she recommends actively seeking feedback and reflecting on each project to gain insights that can develop your skills, along with investing in more traditional learning opportunities when possible. Finally, she highlighted the value of finding your freelance tribe for community, accountability, and support – whether that's through local groups or professional organisations like EMWA.

Breakout rooms

After Eleanor's presentation came the most interactive part of the FBF, the table discussions. Since the forum occurred on Zoom, this meant online breakout rooms. Each room had a specific topic with moderators leading the conversation (Figure 1). Attendees switched freely between rooms, and after 45 minutes, the discussions ended and each moderator shared a summary of

their group conversation with all attendees. The summaries are listed below.

Breakout room 1:

Hybrid work: juggling freelancing with part-time employment

Kfir Lapid led the conversation on the hybrid work model in this breakout room. He had already been a part of a panel discussion on this topic in the FBF at the Spring EMWA Conference in Valencia, as it was such a popular subject. Hybrid work combines the security of a traditional job (part-time employment) with the flexibility of freelancing. Kfir shared his experience of freelancing as a temporary solution when transitioning from academia to industry. However, after landing a permanent job, he realised he could not give up his freelance business and became a hybrid worker. He explained that while freelancing is typically more flexible, the employee role is more predictable. One attendee likened it to employment being the cake and freelancing being the icing.

Kfir noted that it can be difficult to find a part-time position that allows for freelancing side activities, but he advised medical writers to be upfront about their freelancing plans in job interviews. He believes that prospective employers truly interested in hiring you will understand. In some part-time positions, such as teaching, employers would probably not care if the teacher has other side jobs. Being a hybrid worker also helps medical writers gain knowledge and transferable skills from both worlds, making them even more valuable for employers and freelance clients alike.

Breakout room 2:

The relationship between CROs and freelancers – how do they work and how do you get started?

Andrew Balkin guided a discussion on how freelancers can work with contract research organisations (CROs). He shared proactive steps that freelancers can take before, during, and after initially reaching out to CROs, and exactly when, why, and what to say/write/include in that email. Some CROs source freelancers through recruitment agencies, while others have in-house recruitment departments. For the latter, a generic email could fall into an abyss, so Andrew shared tips and tricks on how to identify the right contact person and increase the chances of getting work. Being listed in the EMWA freelance directory is also useful as this is used/searched by many companies. Additionally, your CV must match your LinkedIn profile. While this may seem obvious, this is often overlooked.

The conversation also covered what types of freelance help CROs may need. Since the demand for freelancers can vary with workload highs and lows, there will be times when CROs particularly need extra help, especially under tight deadlines. Many freelancers have specialist experience that CROs may lack in-house, such as expertise in certain document types, conditions, etc., which can be important for securing work. Lastly, attendees discussed how often freelancers should reach out to the same CRO for work. While there's no clear answer, maintaining contact rather than just reaching out once can lead to more opportunities in the future.

Breakout room 3:

From freelancer to small business owner

Katrin Zaragoza Dörr went from freelancer to small business owner herself and started a conversation about the different ways to create and run your own company, which can vary between countries. If based, for example, in Spain, you might choose to be a freelancer only or create an LLC (limited liability company) to protect your personal assets. In the UK, however, a freelancer must work under an LLC umbrella company. Some people also consider forming an LLC for tax benefits, so it's a good idea to consult an accountant and/or a tax advisor to understand the financial advantages.

Different options for operating as an LLC were also discussed, such as whether to employ yourself or invoice your LLC, and whether to hire medical writer employees or subcontract to freelancers. Katrin advised anyone with any further questions about setting up a business to explore the EMWA entrepreneurship-SIG, which offers the opportunity to learn from established business owners (see https://emwa.org/sigs/entrepreneurship-sig/).

Breakout room 4:

Managing multiple projects and overlapping timelines as a freelancer

Archana Nagarajan led the discussion about managing multiple projects and overlapping timelines – a challenge for every freelancer. Many in the conversation shared their favourite tools and strategies to keep track of multiple projects and meet deadlines. This included project management tools/software such as Monday, Freedcamp, Things (only for Mac), and ClickUp. More useful software included Calendly (for scheduling meetings), Google Calendar, Google Notes, Sorted (for invoices and taxes in Germany), and Toggle (timer).

To save time, it's useful to create email templates for certain tasks, which can be made using artificial intelligence (AI). It is also helpful to provide a structured list of questions and checklists for any documents needed from the client. Finally, keeping track of how much time is spent on each project can help freelancers provide better quotes for future projects.

When it comes to working with clients, it is sometimes necessary to push project deadlines and it is crucial to be upfront and honest about this. If freelancers are working with the same client on various projects, they must always ask about the priority level and flexibility for each project to avoid any future complications. Ultimately, everyone agreed that maintaining good communication with the client is key to a successful project.

Closing events

At the end of the discussions, each moderator shared a summary of their group conversation with all attendees.

Adriana closed the event, thanking all the volunteers who kindly shared their time and expertise, as the FBF would not happen without them, and expressed her wishes to see everyone face-to-face in Riga at the May 2025 conference.

Breakout rooms	
1. Hybrid work: juggling freelancing with part-time employment	**Kfir Lapid**
2. The relationship between CROs and freelancers – how do they work, how do you get started	**Andrew Balkin**
3. From freelancer to small business owner	**Katrin Zaragoza Dörr**
4. Managing multiple projects and overlapping timelines as a freelancer	**Archana Nagarajan**

Figure 1. Breakout rooms: topics and moderators

The Crofter: Sustainable Communications

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Editorial

Greetings from the croft. At the 2024 hybrid Autumn EMWA conference, the Sustainability Special Interest Group (SUS-SIG) team was delighted to host our second expert seminar series. In this issue, Sarah shares a few highlights from the session, which offered glimpses of hope and inspiration against the background of the climate crisis. Medical writers emerge as pivotal figures in communicating on the environmental impact of healthcare. We hope all our speakers and audience members enjoyed the session as much as we did, and look forward to running other seminars in the future!

Best,
Sarah and Louisa

Sustainability in healthcare: Updates and insights for medical writers

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Abstract

The 58th EMWA Conference last Autumn was the occasion of the second Sustainability Special Interest Group (SUS-SIG) expert seminar series. Our six panellists joined in a lively and thoughtful discussion with enthusiastic participants. The recording will soon be available to EMWA members on the SUS-SIG website found at emwa.org. In this article, I have summarised the key take-aways from the session, provide links to useful resources, and recap our panellists' invaluable tips on how to greenify your IT tasks.

At the hybrid EMWA conference in November 2024, EMWA's Sustainability Special Interest Group (SUS-SIG) hosted its second expert seminar series (ESS), featuring one returning speaker and introducing many new ones. We delivered this seminar to showcase the growing motivation among the healthcare community to reduce the negative environmental impacts of healthcare. We were delighted to host speakers working at the forefront of durability and sustainability in healthcare, providing the viewpoints of biopharmaceutical and clinical research organisations, academia, and public health experts.

Changing perspectives and terminology

Amy Booth from the Nuffield Department of Primary Care Health Sciences at the University of Oxford, England, opened her talk by highlighting how the healthcare industry's environmental impacts reach far beyond climate change alone. To illustrate this, she presented a case study of how antibiotic-treated cow carcasses caused deadly kidney disease and population decimation of scavenging South East Asian vultures;[1] this, in turn, lead to downstream impacts that caused the deaths of half a million people – an important reminder of how pharmaceutical products can have unforeseen ecological consequences.

An interesting take-away from Amy's talk was the changing fashions of environmental goals and terminologies. Previous targets such as "carbon neutral" and "net zero" are falling out of favour in preference for "real zero", which is a more stringent measure, includes all greenhouse gases, and cannot be reduced through off-setting.

Motivation to change in large companies

David Lumby from PPD, Thermo Fisher Scientific's Clinical Research Group provided fascinating insights into the ways that a large clinical research organisation approaches sustainability. On the topic of decentralised trials, previously covered in *Medical Writing*,[2] he highlighted a beneficial impact on sustainability, as participant retention rates are higher and sample sizes can be reduced. He also touched on the lower carbon footprint of clinical trials in Europe than in America, attributing this – partially – to clinical research associate trips that are more frequently taken by train in Europe than in the USA.

Climate impacts in Africa and a call-to-action to medical writers

Gomotsegang Fred Molelekwa from Tshwane University of Technology, South Africa, next talked about the roles that medical writers could play in raising awareness of environmental sustainability in

Africa. He noted that medical writers were perfectly placed to act as agents of change for sustainable healthcare in Africa, and urged us to: "Be at the forefront of advocacy initiatives pertaining to sustainable procurement in public and private healthcare sectors".

He suggested further reading on websites such as South Africa's Education for Sustainable Healthcare initiative (https://saahe.org.za/education-for-sustainable-healthcare) and the WHO's Alliance for Transformative Action on Climate and Health (https://www.who.int/initiatives/alliance-for-transformative-action-on-climate-and-health).

Ambition Zero Carbon and green IT

Claudia Percivalle outlined AstraZeneca's route towards achieving "ambition zero carbon" through a multi-pronged approach combining

life cycle assessments, safe active pharmaceutical ingredient discharge, and ecopharmacovigilance tracking, amongst others. She also shared her top five tips for incorporating green IT into daily working practice (Figure 1). These prompted wincing among the participants as we recognised some of our own bad habits (don't we all leave our PC on standby overnight every now and then?). Claudia's suggestions are straightforward and easy to follow, so if you, too, spot some areas to improve, try and implement at least one this week, and pass on tips to your colleagues!

Green posters and hope for the future

During the panel discussion, **Gemma Rogers** described Oxford PharmaGenesis' sustainable solution to conference posters. She recounted having successfully switched from paper posters to fabric-printed ones which can be washed and reused. An added benefit: fabric posters are foldable and easy to transport! Gemma also highlighted a recent study, co-led by Oxford PharmaGenesis and the Nuffield Department of Primary Care Health Sciences, on how pharmaceutical companies reduce their greenhouse gas emissions.[3]

1. Use links when sharing documents not attachments
2. Shut down your laptop every day
3. Reduce length of time storing Microsoft Teams' recordings
4. Reduce printing
5. Reduce storage

Figure 1. Claudia Percivalle's green IT tips to put into place immediately

Our expert panel also discussed lean writing strategies, where a focused effort is made to minimise the size and number of documents, and the My Green Lab freezer challenge, a good motivator to audit freezer contents and save energy. To get in on a chance to win a plaqueand certificate, it is not too late to sign up for the 2025 competion, open to labs of all sizes: https://www.mygreenlab.org/freezer-challenge.html

Amid all the bad news on the climate crisis, panel members all gave reasons to be optimistic for the future. Amy noted that the people she works with are increasingly familiar with the terminology and issues at stake, indicating that messaging around green initiatives is reaching ever-broader audiences. Fred gave some examples of green energy initiatives in various hospitals and universities in Africa.

The three-hour seminar flew by and could easily have continued for another three. It is clear that there will be plenty of material to cover in a future ESS! A recording of the session should be available soon on the SUS-SIG section of the new EMWA website for those that were not able to attend.

SUS-SIG member and ESS co-host Catarina Leitao wrapped up the meeting with a quote from Jane Goodall, which I finish with here as an inspiring message for us as medical writers and habitants of planet earth: "A great deal of our onslaught on Mother Nature is not really lack of intelligence but a lack of compassion for future generations and the health of the planet (...) True wisdom requires both thinking with our head and understanding with our heart."[4]

> Be at the forefront of advocacy initiatives pertaining to sustainable procurement in public and private healthcare sectors.

Acknowledgements

I would like to thank Kimi Uegaki for planning the ESS, Louisa Ludwig-Begall and Catarina Leitao for their invaluable help in organising and running the event, and Raquel Billiones for constant support. I am very grateful to our wonderful speakers and panellists of the ESS.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. Cook SE, Green RE, Lieberherr E, et al. Current policies in Europe and South Asia do not prevent veterinary use of drugs toxic to vultures. Ecol Solut Evid. 2024;5(2):e12357. doi:10.1002/2688-8319.12357
2. Mackinnon J. Bringing decentralised clinical trial protocols to life. Med Writ. 2023;32(1):12–8. doi:10.56012/rtqr5570
3. Booth A, Jager A, Faulkner SD, et al. Pharmaceutical company targets and strategies to address climate change: content analysis of public reports from 20 pharmaceutical companies. Int J Environ Res Public Health. 2023;20(4):3206. doi:10.3390/ijerph20043206
4. Goodall J, Abrams DC, Hudson G. The book of hope: a survival guide for trying times. First edition. New York, NY: Celadon Books; 2021. 252 p. The global icons series.

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CONTACT US

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

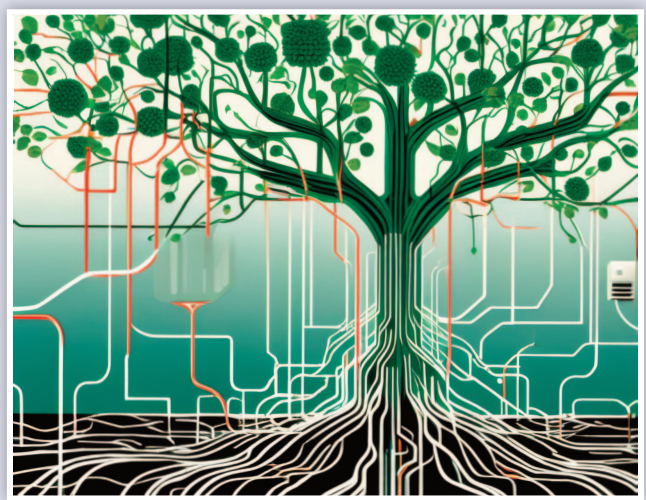
Upcoming issues of **Medical Writing**

June 2025:

Communicating with the Public

When we communicate effectively with patients and the public, we empower them to make informed decisions about their health. This issue will cover the latest guidelines and standards to be considered when writing and designing information for patients and the public. It will also feature articles from thought leaders on plain language writing, inclusive communication, and patient involvement in research. With this issue, we hope to provide insights that will strengthen the role of medical writers as advocates for the patient voice, and as powerful and effective communicators of understandable science.

Guest Editors: Sampoorna Rappaz and Lisa Chamberlain James
The deadline for feature articles has now passed.



September 2025:

Real World Data/Real World Evidence

Real-world data and real-world evidence have become integral to medical research and healthcare decision-making. Their value lies in providing insights into how healthcare treatments and interventions perform in everyday settings, which can differ significantly from controlled clinical trial environments. This issue of Medical Writing will include a broad range of articles on the issue theme covering critical aspects for medical writers working with these types of data.

Guest Editor: Maria Kołtowska-Häggström and Laura Collada Ali
The deadline for feature articles is June 1, 2025.

December 2025:

Safety Writing

As the regulatory landscape continues to evolve, the importance of precise and thorough safety reporting has never been more critical. This issue will provide insights into the latest methodologies, best practices, and innovative approaches that are shaping the future of safety writing. The issue will feature articles on the development and submission of safety data, offering expert guidance on handling complex safety data.

Guest Editors: Iva Cvetkovic and Pavle Simeunovic
The deadline for feature articles is September 1, 2025.